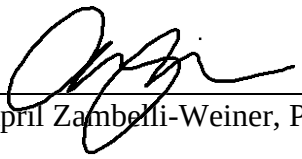
EXHIBIT C8

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF APRIL ZAMBELLI-WEINER, PHD, MPH

Date: November 16, 2018



April Zambelli-Weiner, PhD, MPH

Expert Report of April Zambelli-Weiner, Ph.D., M.P.H.

16 November 2018

Table of Contents

List of Tables

Acronyms and Key Terms

ACE	American College of Epidemiology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
FDA	Food and Drug Administration
H&M	Huncharek and Muscat
IARC	International Agency for Research on Cancer
J&J	Johnson & Johnson
M-H	Mantel-Haenszel
MPH	Master of Public Health
NIH	National Institutes of Health
OR	Odds Ratio
PCPC	Personal Care Products Council
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized Controlled Trial
ROB	Risk of Bias
RR	Relative Risk
TTi	TTi Health Research & Economics

1 Qualifications

My name is April Zambelli-Weiner. I am an Epidemiologist with a PhD in Epidemiology and Human Genetics from the Johns Hopkins Bloomberg School of Public Health. I received my Bachelor of Arts in Chemistry and English from Washington & Jefferson College and a Master of Public Health (MPH) in Epidemiology/Community Health from Saint Louis University. I am the President and founder of TTi - Health Research & Economics (TTi). Attached hereto as Appendix C is a copy of my current curriculum vitae.

I am a methodological expert in epidemiology and public health and health care research methodology. This includes but is not limited to the design of epidemiological studies, the collection and analysis of epidemiological data, the appropriate application of statistical methodology to research questions, and evidence synthesis involving analysis and synthesis of knowledge from other scientific disciplines such as biology, toxicology, and medicine.

My expertise is based on my training; my more than 20 years of experience; and my reading, mentoring, publishing and work in applied epidemiologic research. My direct epidemiologic experience has included a wide range of projects that vary in size, scope and methodology. I have participated in the design and implementation of large clinical, population and family-based studies, including the collection of primary data in clinical settings and in the field; I have analyzed data from large clinical and administrative databases as well as data from national surveys and disease registries; I have performed methodological reviews of proposed studies and conducted research as part of my routine work for both public and private clients; I have conducted extensive literature reviews and routinely perform meta-analyses. I have had the opportunity to participate in and lead projects that shape critical health programs and resources at the Federal level, including work for the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH). My work has generally focused on diseases and outcomes that impose a substantial burden on public health, including chronic diseases such as cancer. Much of my work has involved evaluating the efficacy, safety, effectiveness and cost-effectiveness of clinical and public health interventions, including drugs, devices, health care services and procedures and public health programs.

My company, TTi Health Research & Economics, is a research and consulting firm serving a diverse clientele that includes contracting with federal Health and Human Service Agencies like CDC and NIH as well as private entities, including pharmaceutical, medical device and biotechnology companies and manufacturers of personal care products. As part of my routine work for private clients, I have participated in the design of clinical studies, including post-market studies, conducting evidence synthesis, including meta-analysis, and performed evaluations and methodological reviews of proposed and conducted research.

As an epidemiologist, much of my work has focused on diseases of inflammation. Inflammation is known to underlie a wide range of chronic conditions, including cancer, asthma, and diabetes, among others. My work over the last 20 years has focused on understanding and preventing chronic disease. My company currently holds a five-year contract with the National Center for Chronic Disease Prevention and Promotion at the Centers for Disease Control and Prevention (CDC) to provide a wide range of services related to epidemiological study design, statistical analysis, evaluation of health interventions, health communications and complex modeling, among others.

2 Assignment

In 2008, Samuel Epstein, MD of the Cancer Prevention Coalition (CPC) filed a Citizens Petition with the FDA with respect to talcum powder cosmetic products like Johnson & Johnson's (J&J) Baby Powder and Shower to Shower powder. The CPC requested that the FDA require that a warning be added to personal care products containing talc regarding the risk of ovarian cancer. In addition to requesting a hearing before the FDA, the CPC requested that the FDA "Immediately require that cosmetic talcum powder products bear labels with a prominent warning such as 'Frequent talc application in the female genital area is responsible for major risks of ovarian cancer.'" That petition was based primarily on the then existing epidemiologic studies.

On July 29, 2009 the talcum powder industry, including J&J and Imerys, submitted a report to the FDA (vis-à-vis the Personal Care Products Council (PCPC) in response to a Citizens Petition. The industry's report was entitled "Comments on Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products" and was authored by Drs. Michael Huncharek and Joshua Muscat of Meta-Analysis Research Group. That report was provided by industry to the FDA to "provide an independent review of the data."

I have been asked to address the methodology of the 2009 Huncharek and Muscat (H&M) Report submitted to the FDA and the subsequent 2011 publication and representations made by the authors on behalf of the talcum powder industry to FDA and the medical and scientific community.[1]

3 Summary Opinion

The 2003 Huncharek Meta-Analysis and 2007 Huncharek Diaphragm study contain substantial errors, including misstatements of underlying data, improper calculations, and do not utilize

[1] I have not been requested to do a full causal assessment of the scientific evidence on talc exposure and risk of ovarian cancer.

generally accepted methodologies and best practices in epidemiology and meta-analyses rendering the findings flawed and unreliable. These studies were heavily relied on by the Talc industry in its 2009 submission, written by Drs. Huncharek and Muscat, to FDA in opposition to a Citizen's Petition requesting that an ovarian cancer warning be required on talcum powder products. These errors were re-published in a 2011 review paper by Drs. Huncharek and Muscat. Any scientific, regulatory or policy deliberations or decisions, including but not limited to those undertaken and issued by the FDA, that relied upon the data and analyses put forward by Drs. Huncharek and Muscat, in whole or in part, are based on flawed data, calculations and conclusions.

4 Background Underlying Opinions

THE 2008 CITIZEN'S PETITION TO THE FDA[1]

According to the Code of Federal Regulations (CFR), Title 21 (Food and Drugs), any citizen may file a petition requesting FDA to "issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action." The petition must follow a particular format and, if accepted, is posted online for a review period, during which an interested party may submit comments and the FDA may undertake other procedures, such as meetings and conferences, as part of the review process. On May 13, 2008 Dr. Samuel Epstein, Chairman of the Cancer Prevention Coalition, submitted a petition to the FDA seeking that the FDA "immediately require cosmetic talcum powder products to bear labels with a prominent warning such as 'Frequent talc application in the female genital area is responsible for major risks of ovarian cancer'" [1(p2)].[2] The grounds for this request are summarized as follows:

- 12 publications since 1995 confirming the causal relation between genital application of talc and ovarian cancer, and the protective effect of tubal ligation or hysterectomy, preventing the translocation of talc to the ovary;
- Strength of epidemiology evidence, including a large case-control study [2] and numerous others [3–7] that confirmed the association between perineal talc use and risk of ovarian cancer;
- An analysis of 16 pooled studies confirming a statistically significant 33% increased risk of ovarian cancer associated with perineal talc use
- A report by 19 scientists in eight nations worldwide under IARC confirming a 30-60% increased risk of ovarian cancer following the perineal application of talc

[2] The CPC filed a prior petition on November 17, 1994. As of the date of the 2009 petition, the 1994 petition had not been decided.

THE 2009 INDUSTRY RESPONSE TO THE CITIZEN'S PETITION[8]

In response to the 2008 Citizen's Petition to the FDA, the Personal Care Products Council submitted comments in the form of a report authored by Drs. Michael Huncharek and Joshua Muscat of Meta-Analysis Group on July 24, 2009 (hereafter referred to as the 2009 H&M Report). The work by Drs. Huncharek and Muscat that is represented in the PCPC response was commissioned by Johnson & Johnson (J&J) initially in 2008 and, after edits in meetings with J&J and Imerys (Loretz 425:21-426:1), it was decided that this would be submitted on behalf of the talc industry by PCPC (Loretz 423:9-424:5). According to Dr. Linda Loretz, Director of Safety and Regulatory Toxicology at PCPC, this document would have been sent to the PCPC members for approval before submission (Loretz 425:21-426:1). In 2009, PCPC, J&J and Imerys met with the FDA Office of Cosmetics and Colors and presented the data included in the response to the Citizen's Petition (Loretz 495:4-510:22)[9]. The response was then formally submitted to the FDA in July 2009. The 2009 H&M Report was the only comment received by the FDA in response to the Citizen's petition[3].

The 2009 H&M Report was subsequently published, in part, in 2011 as a review article in the *European Journal of Cancer Prevention.* That article is entitled "Perineal talc use and ovarian cancer risk: A case study of scientific standards in environmental epidemiology," and discloses that the authors were consultants to Johnson & Johnson and Imerys "at the time the initial drafts of this manuscript were produced." At the time of publication, both authors had been retained by Johnson & Johnson as expert witnesses in talc litigation (Muscat 283:18-284:12)[10].

Within both the 2009 H&M Report and the subsequent 2011 review article, Drs. Huncharek and Muscat rely upon two of their own prior studies to support their opinion that the positive association observed between talc and ovarian cancer was non-causal:

> (1) A meta-analysis entitled "Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies" published in 2003 in the journal *Anticancer Research*, hereafter referred to as "2003 Huncharek Meta-Analysis"[11] and
>
> (2) A meta-analysis entitled "Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies" published in 2007 in the *European Journal of Cancer Prevention*, hereafter referred to as "Diaphragm Study."[12]

In fact, these articles and the analyses in them were a primary focus of the arguments advanced by the talc industry in opposition to a mandatory cancer warning on talcum powder products.

[3] https://www.regulations.gov/docket?D=FDA-2008-P-0309

THE HUNCHAREK AND MUSCAT ANALYSES

The accuracy of the 2009 H&M Report and subsequent 2011 review article by Drs. Huncharek and Muscat, and their own studies referenced therein (2003 Huncharek Meta-Analysis, 2007 Diaphragm Study), take on added importance as data on talc exposure and risk of ovarian cancer given how they were represented to the FDA and as the sole evidence submitted in opposition to the Citizen's Petition.

The fact that the 2003 Huncharek Meta-Analysis and the 2007 Diaphragm Study resulted in peer-reviewed publications does not preclude the scientific community from undertaking a thorough critical review of these papers which, when submitted, influenced important regulatory and policy decisions. While these studies are certainly a part of the larger evidence base considered as part of a causal assessment, they assumed added importance from a regulatory and policy perspective due to the fact that the authors attributed added weight to their own publications and prior conclusions as well in advocating them to the FDA in 2009 and the medical and scientific community in 2011.

Because these articles were given added prominence in regulatory proceedings and in a publication by the talc industry, I have been asked to review and assess the validity of data and claims put forward by Dr. Michael Huncharek and Dr. Joshua Muscat. My analysis is focused on the 2009 H&M report to the FDA and the subsequent 2011 publication of that report as well as the following papers which precede the report: (1) 2003 Meta-Analysis, (2) 2007 Diaphragm Study.

5 Methodology

In reaching the conclusions and opinions set forth in this report regarding Huncharek and Muscat's report and publications, I have had access to publicly available documents as well as some produced by Defendants in this litigation, some which were initially provided by Plaintiff's counsel and others I have requested[4]. The information which I have considered is included in the Works Cited. In reaching my opinions, I relied on my more than 20 years of education, training, and experience. As set forth below, in performing my review and analysis and formulating my opinions for this report, I have reviewed the work product of Drs. Huncharek and Muscat and any relevant scientific literature. In doing so I employed methods that are generally accepted by the scientific community and performed my review and analysis in the same manner as I do in the ordinary course of my work as an epidemiologist. The methodological approaches and

[4] I requested additional documents relating to the 2003 and 2007 studies by Huncharek and Muscat, that might have been in the possession of Dr. Huncharek who I understood did the primary analyses. I was informed that Dr. Huncharek has not been made available for deposition and that he claims his documents relating to his work on talc were destroyed in a fire.

considerations that informed my analysis are discussed below, although this is not an exhaustive list.

5.1 EVALUATION AND INTERPRETATION OF EPIDEMIOLOGIC STUDIES

Validity and reliability are the keystones of scientific research. Epidemiology specifically is a science of measurement, where ensuring accuracy and reliability in research is the cornerstone of our profession and the ethical standards by which epidemiologists abide "provide a framework in which scientific quality, rigor, and accountability are enhanced and maintained." [13] Specifically the ethics guidelines from the American College of Epidemiology require a commitment to adhering to the highest scientific standards:

> *Adhering to the highest scientific standards includes choosing an appropriate study design for the scientific hypothesis or question to be answered; writing a clear and complete protocol for the study; using proper procedures for the collection, transmission, storage, and analysis of data; making appropriate interpretations from the data analyses; and writing up and disseminating the results of the study in a manner consistent with accepted procedures for scientific publication.*

The evaluation of individual epidemiological studies involves an assessment of the reliability and internal validity of the study. Reliability is the concept that results must be repeatable; that is, other researchers should be able to perform the same experiment or analysis, under the same conditions, and generate the same results. Internal validity of a study addresses whether a study is able to draw correct conclusions about associative relationships; i.e., "Is the study measuring what it is supposed to be measuring?" [14,15]. An evaluation of internal validity seeks to determine whether observed changes in risk of disease can be attributed to the exposure under study (and/or other variables that are controlled for) and not to other possible causes, such as uncontrolled bias.

Transparency and Reproducibility

The reliability of scientific findings cannot be evaluated if research is not reported in a transparent and reproducible manner. Therefore lack of transparency and reproducibility intrinsically compromises and diminishes the quality of research. True replication often does not occur in observational epidemiology because, by definition, people and populations are highly variable, so creating the same set of conditions is nearly impossible. This is why in the analysis of an epidemiological evidence base researchers seek to evaluate consistency, not replication, which is the same general result in different scenarios. Meta-analysis, on the other hand, is highly amenable to replication. Because meta-analyses have become pivotal to public health, policy and health care decision making, guidance exists on the proper reporting of results from such studies, one example being the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses):

> *Systematic reviews and meta-analyses have become increasingly important in health care. Clinicians read them to keep up to date with their field and they are often used as a starting point for developing clinical practice guidelines…As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting.*[5]

The 2009 paper from the PRISMA group also states: "As is true for all research, systematic reviews should be reported fully and transparently to allow readers to assess the strengths and weaknesses of the investigation" [16]. The importance of transparency and reproducibility in research cannot be over-emphasized. A recent peer-review article summarizes the issue well: "In all cases, transparency in the methods and results of quantitative syntheses is paramount, as is full justification of any choices made." The authors further call for "journal editors and evidence synthesis coordinating bodies to ensure that quantitative synthesis methods are adequately reported in a transparent and repeatable manner in published systematic reviews." [17]

Bias

Bias is defined as systematic error, which can be caused by a variety of flaws in study design, study group selection, and methods used to collect the data [14,18]. Bias is generally caused by factors that create unmeasured differences between the study groups. The major sources of bias include information bias (which includes misclassification bias), selection bias, and confounding [14,15,18]. Information bias may be introduced if the quality and nature of the information elicited from the study groups (cases and controls, or exposed and unexposed) is systematically different. Misclassification bias may occur if the study subjects in one or both of the study groups are systematically misclassified into the wrong group (i.e. case versus control, or exposed versus unexposed). In epidemiology, researchers often cannot enroll the entire population; we have to take a sample. Selection bias can occur when the sampling of study groups is not representative of the entire target population. This can result from the application of different eligibility criteria to the cases and controls [14]. If sampling is representative of the source, or target, population then we can obtain an accurate estimation of the true association. However, if sampling is not representative of the exposure-outcome distributions in the overall population, then the measures of association will be biased, and this is referred to as selection bias.

Confounding

Confounding occurs when a factor is closely associated with both the exposure of interest and the outcome of interest, thereby confusing or distorting the effects of the relationship between the exposure and the outcome [14,15,18]. Otherwise stated, a confounding factor is associated with the disease, and is also correlated with the risk factor under study, but is not a result of the risk factor

[5] http://www.prisma-statement.org/PRISMAStatement/HistoryAndDevelopment

under study. The effect of confounding factors may be controlled by several methods, including matching of the study groups or subjects to each other based on the confounding factors, or statistical adjustment for the effect of confounding factors through stratification or more complicated methods of statistical analysis such as conditional logistic regression [14]. Risk estimates that have taken into account potential confounders are often presented as "adjusted."

5.2 META-ANALYSIS OF OBSERVATIONAL EPIDEMIOLOGICAL STUDIES

A meta-analysis is the aggregation of data and statistics from previously conducted studies through the use of statistical procedures to create a single summary estimate. In a meta-analysis, the unit of analysis is one study and in order to calculate a summary estimate of association, all studies are usually statistically weighted. Meta-analysis typically does not involve the procurement of new data, but relies upon abstraction and synthesis of data reported in published studies and reports. Data abstraction is one of the most important steps in conducting a meta-analysis and its accuracy is paramount to the validity of the analysis. If data is misrepresented from the original studies, the entire analysis is compromised.

Meta-analysis can be an appropriate tool to assist in evaluating the epidemiologic evidence base in situations where there are multiple studies with small sample sizes and/or low statistical power [19]. With the inclusion of multiple studies, a meta-analysis can assist in enhancing statistical power and correspondingly the precision of results. Meta-analysis, however, can also seriously mislead when applied indiscriminately and without consideration of the component studies' designs, variations, and biases [20,21].

Meta-analyses of observational studies have special concerns as compared to meta-analyses of RCTs. The inherent biases in observational studies, such as confounding bias, and differences in study populations and methodologies elevate the importance of thorough qualitative review of the studies, evaluation of the appropriateness of meta-analysis, development of clear inclusion and exclusion criteria that serve the ultimate research question, and careful consideration of sources of heterogeneity across studies that may conflate rather than clarify the research question.

Confounding bias is one of the most important risks to observational studies [20]. Well-conducted epidemiological studies will control for confounding at the design phase (matching) or the analytic phase (multivariate modeling). Combining studies that do not control for confounding introduces a known source of bias and heterogeneity into the data.

Heterogeneity in Meta-Analysis

Because meta-analysis is a tool for combining data across studies, consideration of between-study heterogeneity – and sources thereof – is important to appropriate interpretation of findings [20]. Heterogeneity in meta-analysis is defined as any kind of variability among studies [20]. Variability in the patient populations, the study designs, and the way the exposure and outcome are measured, among others, can lead to differences in the risk estimates across studies.

Observational epidemiological studies differ fundamentally from randomized controlled trials in that they are natural experiments: events are observed as they occur in the real-world, not in highly monitored environments. Because of this, observational epidemiological studies addressing the same research question can vary greatly in the populations being studied and can exhibit inconsistencies in study methods, such as how the exposure and outcome are measured, or defined, and the types of statistical analyses that are conducted (and therefore the results that are presented), among others.

In fact, part of the process of evidence synthesis is an assessment as to whether a quantitative pooling of data, such as meta-analysis, is the best approach given the available studies. An in-depth qualitative review of the individual studies may provide sufficient information to conclude that a meta-analysis of all studies may not be useful or, if conducted, should be interpreted with caution. Such a review should consider the individual study designs and the extent to which they minimize bias and confounding. Alternatively, initial meta-analysis may demonstrate significant heterogeneity across studies. Specifically, statistics that are calculated as part of a meta-analysis measure heterogeneity and may reveal that the studies are not similar enough, such that simply combining them may not be the best approach.

Measuring Heterogeneity. There are different statistics that can be used to assess heterogeneity in a meta-analysis. The I-squared statistic is one of the most common measures of heterogeneity and provides an estimate of the percent of the variability in effect estimates that is due to heterogeneity between studies rather than sampling error (i.e., chance) [20]. I-squared values range from 0% to 100% and increasing I-squared values correspond to increasing heterogeneity between studies [22]. An I^2 of 50% or greater is the threshold for significant heterogeneity [20].

Strategies for Dealing with Heterogeneity. There are numerous ways to attempt to address heterogeneity in a meta-analysis including: exclusion of studies, use of a random effects meta-analysis and conduct of sensitivity analyses to explore sources of heterogeneity [20]. Studies may be excluded from meta-analyses when they do not meet the specified inclusion and exclusion criteria or when there is clinical or methodological diversity. Random effects models provide a statistical tool to address between study heterogeneity in the way the confidence limits of the pooled estimate are calculated. Sensitivity analyses, including subgroup analyses, are used to explore potential sources of heterogeneity and to check the robustness of the primary findings to key methodological decisions.

Sensitivity Analyses

Sensitivity analyses are routinely conducted as part of clinical and epidemiological research [23,24]. The general purpose of conducting sensitivity analyses is to evaluate the robustness of the study's findings to important methodological decisions that can potentially influence the results [20]. Subgroup analyses are a type of sensitivity analysis intended to assess whether the effect estimate

is similar across specified groups of subjects or studies. Subgroup analyses reduce the evidence base to meaningful subgroups and pool data across those subgroups to examine potential differences in effects and to explore potential sources of heterogeneity. Sensitivity analyses are contextually specific, meaning they will vary based on the research question, the type of studies contributing to the evidence base, and the key methodological issues within a particular evidence base.

6 Analysis

6.1 HUNCHAREK ET AL. 2003 (HUNCHAREK META-ANALYSIS)

In 2003, a meta-analysis study by Huncharek, Geshwind and Kupelnick entitled "Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies" was published in *Anticancer Research*. [6] The paper's stated objective was to employ meta-analysis to "evaluate this suspected association." The paper claims to use meta-analytic techniques described in a 1996 paper by Sander Greenland[7] to conduct three analyses that are repeatedly referenced by Drs. Huncharek and Muscat in the papers and report that follow this 2003 study: (1) an overall meta-analysis of the available epidemiological studies[2,3,25–38]; (2) a dose-response analysis[3,25–28,31,33,35,36], and (3) a subgroup meta-analysis that examines heterogeneity by type of controls in case-control studies (i.e., hospital-based versus population-based).

My critical review of this paper revealed a significant number of both superficial and substantive errors, methodological concerns, and a lack of transparency in both methods and reporting that calls into question the accuracy, validity and reliability of the results of this study.

1) Errors in 2003 Huncharek Meta-Analysis Paper

A thorough review of the Huncharek 2003 paper revealed a concerning number of errors – both superficial (typographical and grammatical) and substantive – which undermine the reliability of this study. Most serious of these errors is that data from the original studies, upon which the authors then rely, was incorrectly abstracted for five out of the nine studies listed in Table II of the

[6] It is my understanding that this meta-analysis was proposed to J&J in October 2000 (JNJ000017587) and that the "Preliminary Results" of this study were sent to J&J in November 2000 (JNJ000017613). It is also my understanding that J&J employees made comments to this preliminary draft (JNJ000377405).

[7] This appears to be a reference error in the Huncharek 2003 publication; the Greenland article listed in its reference list was actually published in 1987, not 1996. This is one of several such errors in this paper. See Footnote 8 below.

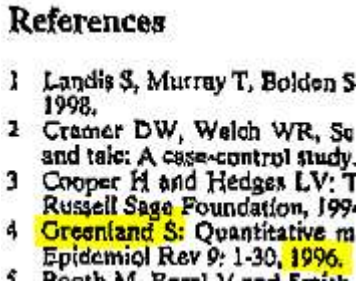
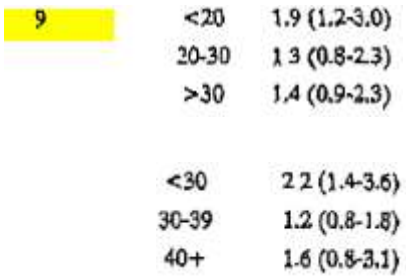
2003 Huncharek Meta-Analysis paper. A list of substantive errors is provided in Table 1 of this report (below)[8].

Table 1. Errors Identified in Huncharek et al. 2003

Excerpt with Error‡	Error Explanation	Location of Error
"Literature retrieval was performed by previously described methods (8)."	*Incorrect reference* No literature retrieval methods discussed in reference 8; therefore no method provided/substantiated (can't be replicated).	Pg. 1956; Paragraph 2; Lines 1-2
for review (2,5-20). Further review showed that the paper by Hankinson *et al.* (12) used the same data as a subsequent paper by Gertig *et al.* (10) from the same laboratory. Therefore, only reference 12 was included in the meta-analysis. The remaining sixteen papers met protocol specified inclusion criteria.	*Reporting error* Says Hankinson was included in the meta-analysis, and Gertig is removed. However, Hankinson is not in Table I of Huncharek, while Gertig is in Table I.	Pg. 1956; Results Section; Paragraph 1; Lines 3-7
Categories of talc application per month: 1x 0.7 (0.3-1.8) 4x 2.0 (1.3-3.4) 30x 1.3 (0.8-1 9)	*Incorrect/missing exposure categories* Booth et al, 1989 reports talc application in categories of "Never, Rarely, Monthly, Weekly, and Daily". Table II in Huncharek does not report the lowest exposure category of Rarely or <1x, OR=0.9 (0.3-2.4).	Table II, Reference 5

[8] A number of typographical and grammatical errors were also found, which can and do occur in research publications; however the number of errors identified in this paper raise concerns about the rigor of the authors quality control procedures and the editorial review process for this journal. For example, published is spelled incorrectly on page 1955; heterogeneity is spelled incorrectly on page 1957; there is incorrect subject verb agreements on page 1958.

8 0-5.5 1.8 (0.9-3.5) 5.5-13.5 1.6 (0.9-2.9) 13.5-27 1.2 (0.6-3.4) >27 1.8 (0.9-3.4)	*Incorrect/missing exposure categories* Cook et al, 1997 reports exposure categories by lifetime days, categories do not overlap. Huncharek exposure categories overlap, and categories are rounded incorrectly if you extrapolate lifetime days to years.	Table II, Reference 8
4-24 0.99 (0.67-1.46) >/=30 1.12 (0.82-1.55)	*Incorrect/missing exposure categories* Not all exposure categories are reported. Those missing from the Gertig et al, 2000 article include: Never and <1x/week, which had RRs/CIs of 1.0 (reference) and 1.14 (0.81-1.59), respectively.	Table II, Reference 10
6 <30 1.7 (1.09-2.68) 30-40 1.44 (0.96-2.15) >40 0.96 (0.54-1.38)	*Wrong reporting of data from original studies.* In Chang et al, 1997 >40 OR is 0.865 not 0.96; <30 upper CI is actually 2.64 not 2.68.	Table II, Reference 6
8 0-5.5 1.8 (0.9-3.5) 5.5-13.5 1.6 (0.9-2.9) 13.5-27 1.2 (0.6-3.4) >27 1.8 (0.9-3.4)	*Inaccurate reporting of data from original studies.* Highlighted CI is actually (0.6-2.4) in Cook et al, 1997	Table II, Reference 8
15 .1 2.0 (1.0-4.0) 1-4 1.6 (1.1-2.3) 5-9 1.2 (0.8-1.9) 10+ 1.2 (1.0-1.5)	Ness et al, 2000 exposures listed in meta-analysis for perineal talc exposure actually include talc application to feet.	Table II, Reference 15

	*Wrong reference citation* This article was published in 1987, not 1996. In the 2007 paper it's cited as 1985 in the reference list.	Pg. 1960; Reference 4
"Seven studies included dose-response data stratified by number of talc application to the perineum per month (Table II)."	*Inaccurate reporting* In Table II, only six studies (not seven) list dose-response data stratified by talc application per month.	Pg. 1958; Paragraph 2; Lines 1-3 and Table II
	*Inaccurate reporting of data from original studies* All of the risk estimates from the Cramer et al. 1999 paper have been rounded, without explanation. For example, original paper has an additional significant digit (e.g., <30 RR is 2.21 vs. 2.2 reported in the Huncharek paper).	Table II, Reference 9
‡Errors from the Huncharek 2003 Meta-Analysis are abstracted and highlighted in yellow for ease of review.		

As discussed in Section 5.1 of this report, careful and accurate abstraction of data from the original studies underlying a meta-analysis is paramount to the validity of the meta-analysis. Because meta-analysis involves weighting of the data from the underlying studies, even small errors in abstraction can become amplified, particularly if a study is given more weight.

In his deposition, Dr. Muscat was asked about the data abstraction errors in Table II from the 2003 Dose Response Meta-Analysis, as reported above in Table 1 of this report. Although he claimed to not have performed this analysis himself (it was done by Dr. Huncharek), Dr. Muscat suggested that the discrepancy between the data reported in the original papers and the data ascribed to those papers in the Huncharek article was as follows: the original papers reported *adjusted* risk estimates (i.e., control for confounding) and the Huncharek analysis used *unadjusted* estimates (i.e., no

control for confounding). As example, in his deposition, Dr. Muscat specifically discussed the error in the data abstracted from the Cook 1997 paper, whereby the upper limit of the confidence interval for the exposure category of 13.5-27 years of talc use is incorrectly reported as 3.4 instead of 2.4. When asked if this was a mistake, Dr. Muscat replied:

> *That's not a mistake. The meta-analysis was based on unadjusted. If there are differences, that's probably the reason why, because the meta-analysis technique is based upon the – the unadjusted numbers rather than the adjusted published numbers (Muscat 478:12-479:2).*

In consideration of this possibility, unadjusted risk estimates were calculated and they still do not match [See Appendix B]. In fact, the unadjusted risk estimate and 95% confidence interval for the Cook 1997 paper is 1.59 (0.84-2.98) – not even close to the values used in the Huncharek 2003 Meta-Analysis. The importance of this is that many of the numbers reported in Table II of the Huncharek 2003 Dose-Response Meta-Analysis are neither the correct adjusted numbers from the original study nor unadjusted estimates as claimed. The table in Appendix B clearly demonstrates that not a single value reported in the 2003 Huncharek Meta-Analysis Table II is an unadjusted value, as described by Dr. Muscat. Further, if unadjusted estimates were used the authors should have described this explicitly in the paper. Instead, the paper's methods describe use of adjusted measures and report adjusted measures in both Tables I and II:

> *Because the variance estimates are based on **adjusted measures** of effect and on the 95% confidence interval for the **adjusted measure**, the confidence interval methods do not ignore confounding and are the preferred methodology for observational data (Huncharek 2003, p1956; emphasis added.*

Inaccuracy and misrepresentation are considered violations of generally accepted standards of research. The implications of the numerous substantive errors and omissions in the 2003 Huncharek Meta-Analysis is that the results are unreliable.

2) Lack of Replication – 2003 Huncharek Meta-Analysis

In their 2003 paper, Drs. Huncharek and Muscat claim that their calculations suggest an inverse dose-repose relationship which argued against a causal inference since they reported that a higher risk was reported with the lowest dose exposure category and lower risk was associated with the highest dose exposure category. Specifically, they report the following summary risk estimates for their dose-response analysis, derived from data in Table II of their study:

Lowest Exposure Category: 1.83 (1.55-2.15)

Highest Exposure Category: 1.21 (1.00-1.45)

Aside from using the incorrect data from the underlying studies as detailed in Section 6.1.1, the exposure category numbers above cannot be replicated. Table 2 of this report (below) shows the results of attempted replication of the numbers above based on the methods as described in the 2003 Huncharek Meta-Analysis and in deposition [10].

The following conclusions can be reached from the data in Table 2 below:

1) No method produces a summary risk estimate of 1.83 for the lowest exposure category;

2) The model that most closely approximates the summary risk estimate of 1.21 for the highest exposure category involves mixing measures of frequency and duration, which is neither generally accepted methodology nor what the authors describe in their manuscript and in deposition;

3) When a standard statistical software package is utilized for the meta-analysis the inverse dose-response relationship claimed by the authors nearly disappears, with the adjusted data for the number of talc applications per month actually showing data suggesting a positive dose response.

Table 2. Lack of Replication of Dose-Response Analysis from Huncharek et al. 2003

		HUNCHAREK AND MUSCAT METHOD (Manual)		GREENLAND METHOD (Manual)		FIXED EFFECTS (Stata)‡	
Analysis	**Studies included (n)**	**Pooled OR, 95% CI Lowest Exposure Category+**	**Pooled OR, 95% CI Highest Exposure Category++**	**Pooled OR, 95% CI Lowest Exposure Category+**	**Pooled OR, 95% CI Highest Exposure Category++**	**Pooled OR, 95% CI Lowest Exposure Category+**	**Pooled OR, 95% CI Highest Exposure Category++**
Mixed exposure							
Unadjusted	9	1.37 (1.05-1.69)	1.24 (1.01-1.48)	1.37 (1.21-1.53)	1.24 (1.13-1.36)	1.17 (0.97-1.37)	1.18 (1.04-1.32)
Adjusted		1.38 (1.05-1.71)	1.21 (0.96-1.45)	1.38 (1.21-1.55)	1.21 (1.08-1.33)	1.18 (0.96-1.40)	1.14 (1.00-1.28)
Applications /month							
Unadjusted	6	1.38 (1.01-1.76)	1.24 (0.90-1.58)	1.35 (0.96-1.74)	1.40 (1.03-1.77)	1.15 (0.92-1.39)	1.19 (0.97-1.40)
Adjusted		1.42 (1.03-1.80)	1.27 (0.92-1.63)	1.42 (1.22-1.61)	1.34 (1.16-1.51)	1.22 (0.96-1.48)	1.20 (0.98-1.42)
Years of talc use							
Unadjusted	7	1.47 (1.08-1.85)	1.24 (0.98-1.50)	1.47 (1.08-1.86)	1.28 (0.96-1.60)	1.35 (1.07-1.63)	1.16 (1.00-1.31)
Adjusted		1.52 (1.11-1.92)	1.18 (0.90-1.45)	1.52 (1.32-1.72)	1.18 (1.04-1.31)	1.34 (1.04-1.63)	1.11 (0.95-1.26)

‡Mantel-Haenszel
+ Compare to 1.83 (1.55-2.15) as reported in Huncharek 2003
++ Compare to 1.21 (1.00-1.45) as reported in Huncharek 2003

Methods Summary: Meta-analytic techniques were employed in an attempt to replicate the dose-response analysis derived from Table 2 of the Huncharek 2003 paper. Numbers presented in Table 2 were used as reported, despite known errors, given the goal of replicating the analysis presented in the paper. Given the limited description of their methods, coupled with possible discrepancies revealed in the deposition of Dr. Muscat, three different exposure permutations were considered (mixing measures of frequency and duration; just studies that examined frequency; and just studies that examined duration). Analyses were also run using both unadjusted and adjusted risk estimates. Three different models were considered: (1) the inverse-variance method described by Huncharek and colleagues in their 2003 paper, (2) the Greenland method cited by the authors and (3) the Mantel-Haenszel (M-H) fixed effects method, which is the default fixed effect method in Stata and in RevMan, used by the Cochrane Collaboration [39].

Clearly the stated methods were not properly employed or the same result would have been obtained using the data as reported in their Table II.

Not only are the numbers incorrectly abstracted from the original studies and the stated methods not properly employed, the choice to employ an inverse variance approach and to execute it *by hand* (Muscat Deposition: 95.1-2), despite the complexity of the calculations that necessitate the use of computer software, is questionable on multiple levels. Statistical packages for meta-analysis were widely available and in use at the time of these analyses. Doing such an analysis *by hand* leads not only to errors, but to lack of transparency and reproducibility concerns. Methodologically, it has been well known in the field of epidemiology since the 1980's (if not earlier) that there are more appropriate, generally acceptable methods for arriving at a pooled, summary risk estimate when sample sizes are small, as is the case here (in the individual exposure strata across many of the studies used in the Huncharek 2003 dose-response analysis).

In his deposition, Muscat states that the dose-response analysis presented in Table II was based on the frequency per month measure. Interestingly, when a standard statistical package is used to replicate that analysis, the results for the frequency per month measure change appreciably, including demonstrating increasing risk with increasing exposure for the analysis using talc applications per month, the opposite of the conclusions drawn by Huncharek and Muscat.

The analyses presented in Table 2 of this report demonstrate that **the dose-response results presented in the Huncharek 2003 paper cannot be replicated based on the data and methods reported in their paper,** further reinforcing the lack of validity and reliability of these analyses. Despite this, and as described further in the report, this data was reasserted to the FDA in 2009 in opposition to a required warning of the potential risk of ovarian cancer and republished to the scientific and medical community in 2011.

3) Other Methodological Concerns

Even if Huncharek and Muscat had executed their dose-response analysis properly and without errors, the entire dose-response methodology is inappropriate and unreliable. A close examination of their analysis reveals a number of methodological errors that undermine their assertion of an inverse dose-response.

On page 1958 of the 2003 article, the authors state that "exposure categories must be roughly similar in order to make valid comparisons across studies." Looking at the dose-response analysis categories, there is overlap between what can fall into the "lowest" exposure categories and the "highest" exposure categories. As example, if an individual had an exposure of 24 applications per month they would fall into the lowest exposure category for two of the studies and the highest exposure category for one of the studies. Having the same levels of exposure in both the lowest and highest exposure categories of a dose-response analysis is completely invalid and would most definitely yield a nonsensical result, as the authors indicate when they state "the available data seem to indicate an inverse dose-response relationship which is counter-intuitive."

In addition, attempted replication of this analysis shows that the exposure categories of duration (years of talc use) and frequency (# applications per month) were likely mixed together[9] (See Table 2 of this report, above), another significant methodological deficiency. The entire objective of meta-analysis is to bring clarity to a research question by combining "like with like." Mixing together different measures of exposure, in this case "frequency" and "duration," violates that primary objective and the assumptions of meta-analysis. In combining two different exposure categories the authors concluded there was an inverse dose-response relationship when they could make no such assertion based upon the analyses they performed.

4) Unsupported Claims of Bias from Uncontrolled Confounding

In the 2003 Huncharek Meta-Analysis, the authors found a "statistically significant result suggesting 33% increased risk of ovarian cancer with perineal talc use." Nevertheless, the authors assert that "uncontrolled confounding" may explain the consistent positive association seen in the epidemiological evidence base on talc and ovarian cancer. In fact, confounding is mentioned six times in the paper, with five of the six being hypothetical statements:

1) *Uncontrolled confounding may result in a spurious positive association between talc and ovarian cancer (abstract).*
2) *Uncontrolled confounding may account for the positive associations seen in prior epidemiological studies (abstract).*
3) *Serious questions remain regarding the validity of this finding, including…the possible presence of uncontrolled confounding producing a spurious positive association (p1955).*
4) *The summary relative risk may in fact be spurious due to bias or uncontrolled confounding (p1958).*
5) *If meta-analyses show that the patterns of low relative risk or odds ratios are elevated across all relevant studies in different populations, these weak associations are less likely to be due to study bias or uncontrolled confounding. Nonetheless, even in this instance, if a bias affects all studies in the same manner, an association may be shown although the finding is spurious (p1960).*

Apart from raising the question, the authors provided no substantive evidence or discussion of the plausible role of uncontrolled confounding in their analysis or the larger evidence base. Based upon their description of their methods it appears that they do not evaluate and/or discuss what the important confounders are to the talc-ovarian cancer research question; they do not assess the

[9]I say likely because the authors do not adequately describe their methods in a clear and transparent way so a reviewer can be certain of what analyses they did. That said, running all possible permutations based on the data provided in their paper, the only model that yields a result similar to what they report involves mixing data on frequency and duration.

adequacy of control for confounding at the individual study-level, nor do they specify any consideration whatsoever of confounding in their meta-analytic protocol.

The authors do not provide any empirical evidence to support their assertion that uncontrolled confounding may explain the observed positive association between talc exposure and ovarian cancer.

As indicated previously, five of the six mentions of confounding have no reference or supporting data. The sixth mention of confounding is in the methods on p 1956 of the 2003 Huncharek Meta-Analysis paper:

> *This meta-analysis method is a general variance-based method employing confidence intervals. Because the variance estimates are based on adjusted measures of effect and on the 95% confidence interval for the adjusted measure, the confidence interval* ***methods do not ignore confounding and are the preferred methodology for observational data.*** *(Emphasis added)*

Despite the stated importance of controlling for confounding according to the methods written in the 2003 Huncharek Meta-Analysis paper, the authors later contradict this assertion, in both their 2009 response to the FDA Citizen's Petition and in deposition, stating that using unadjusted risk estimates (with no control for confounding) would be the appropriate methodology.

The advancement of unsubstantiated claims is a violation of research standards. As example, the influential medical journal *Cancer Medicine* advises researchers in their standards for publication of research under the section "Editorial Policies and Ethical Considerations:" *Cancer Medicine accepts papers that are relevant to our readership and reflect valid science i.e. conclusions drawn need to be substantiated by the data*[10]. In this case, the Huncharek and Muscat conclusions that depend on upon unsubstantiated claims of uncontrolled confounding were invalid and unreliable.

5) Unsubstantiated Claims of Selection Bias & Disregard of Non-Supportive Findings

Similar to the confounding issue above, Huncharek and Muscat offer unsubstantiated claims of selection bias to explain away the positive association between talc and ovarian cancer. In scientific research, unsubstantiated claims are invalid and should not be relied upon. As cited in CFR Title 21, Food and Drugs, Chapter 1 **Food and Drug Administration**, Section 860.7 "Determination of Safety and Effectiveness[11]:"

> ***Reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.***

[10] https://onlinelibrary.wiley.com/page/journal/20457634/homepage/forauthors.html
[11] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=860.7

On page 1959 of their 2003 paper, Huncharek and colleagues state:

> *One possible explanation of the potentially spurious positive association between talc use and ovarian cancer risk is the existence of a "treatment effect" among cases… Some patients with ovarian cancer will undergo treatment with radiation, chemotherapy and/or surgery. Side-effects from treatment may prompt talc use among some patients.*

While a "treatment effect," also referred to as reverse causation by some, is plausible, the authors again provide no substantive evidence or discussion to support this supposition. Huncharek and Muscat later go on to admit that there is no basis for such an effect in the literature in their 2009 Response to the FDA:

> *Compared with controls, ovarian cancer patients report a multitude of symptoms including pain, abdominal bloating and urinary frequency…These factors could contribute to a detection bias where ovarian cancer symptoms could prompt short-term talc use. Although this suggestion is theoretically possible, it has not been addressed in the literature in the context of the talc/ovarian cancer hypothesis (p16).*

The authors also single out this possible bias as a way to explain the consistently observed positive association, omitting a discussion of the implications of such a treatment effect in the hospital-based case-control studies, which they continually rely upon as evidence against a causal association. By definition, hospital-based case-control studies utilize control patients who are sick. Pain, abdominal bloating and urinary frequency are not symptoms that are limited to ovarian cancer. All of these symptoms are exhibited by patients with other conditions – and other cancers specifically. In the Wong 1999 study [25], over 80% of the control population consisted of patients with gastrointestinal cancers and skin cancers – both of which could prompt short-term talc use. Similarly, the control group in the Booth 1989 study[26] included patients with urinary disease, skin disease, gastrointestinal cancers, hemorrhoids, and other disorders with symptoms relating to the gastrointestinal tract and urinary system. If control patients had a higher probability of using talc due to the symptoms of their condition or due to treatment, the net effect of this would be to bias the risk estimate to the null (no association). This is one possible explanation for the attenuated risk estimates observed in the hospital-based case control studies. So while the authors raise the possibility of a treatment effect, they unfortunately present an imbalanced discussion of the potential impact to this evidence base. Furthermore, and perhaps more importantly, they continue to rely upon the purported difference in risk estimates between population and hospital-based case-control studies as undermining a causal association, without ever considering counter-factual explanations for the observed difference – including the implications of their own theory of a "treatment effect."

6) Conclusion

Numerous significant errors, including substantive errors that speak to the very core of a valid and reliable meta-analysis, undermine the findings and conclusions from this study—particularly with

respect to dose-response assertions which are repeatedly relied upon by the study authors, asserted to regulatory agencies and disseminated to the medical and scientific community. Utilizing the methods and data described by the authors, their results cannot be replicated, raising serious questions about the scientific integrity of the study. Utilizing generally accepted methods, the analyses produce significantly different results that refute their position that the association between talc use and risk of ovarian cancer is non-causal. Ultimately, Huncharek and colleagues present an unreliable analysis, including the dose-response data, that is both repeated and relied upon in the 2009 H&M Report to the FDA opposing a required label change for talcum powder products, and again republished in their 2011 paper.

6.2 HUNCHAREK ET AL. 2007 (DIAPHRAGM STUDY)

In 2007, Drs. Huncharek, Muscat and others published a paper in the *European Journal of Cancer Prevention* entitled **"**Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies" (Diaphragm Study). This study was funded by a grant from Johnson & Johnson and Imerys [12].

The objective of the 2007 Diaphragm Study was to address the talc-ovarian cancer research question with better precision and validity by restricting the exposure definition to a route of exposure (i.e., diaphragms) that would allegedly bring the talc in closer proximity to the target organ system. As the authors stated, "the talc-ovarian cancer hypothesis could be tested with better precision and validity if the exposure to the suspected carcinogen was directly to the reproductive tract" (Huncharek 2007, p. 423).

The primary analysis of nine studies[26–33,41] reports a summary relative risk of 1.02 (95% CI, 0.80-1.33). The authors conduct several sensitivity analyses whereby particular studies are dropped from the analysis based on various criteria. The results of the sensitivity analyses present a range of risk estimates (0.67-1.15), of which all of the 95% confidence intervals included the null value. The authors conclude that, "our present report, along with our prior meta-analysis pooling data from studies examining the possible ovarian cancer risk associated with perineal talc dusting does not provide evidence of a causal relationship."

As with the 2003 Huncharek Meta-Analysis, my critical review of this paper revealed a significant number of both superficial and substantive errors, methodological concerns, and a lack of transparency in both methods and reporting that calls into question the accuracy, validity and reliability of the results of this study.

1) Significant Errors in Huncharek 2007 Diaphragm Study

Similar to the Huncharek 2003 paper, a thorough review of the Huncharek 2007 paper revealed a concerning number of errors which undermine the validity of this study. Most serious from a

methodological standpoint is the inaccurate reporting and calculations from the original studies. These objective errors undermine the validity and reliability of this study.

A few examples of objective error include:

- The authors state on page 424 "Table 1 provides an overview of the nine reports included in the meta-analysis" and list Richardson et al (1985) as one of the nine studies; Richardson does not appear in Table 1 nor in any other table or figure in the paper.

- In Table 1, Huncharek 2007, the authors list the following odds ratio and 95% CI for the Booth study: 0.75 (0.85-2.02). This OR and 95% CI do not appear anywhere in the Booth study. Furthermore, this is not a valid confidence interval. The lower bound of the confidence interval cannot exceed the point estimate[12].

A more comprehensive list of errors is provided in Table 3 of this report, below.

Table 3. Errors Identified in Huncharek et al. 2007

Excerpt with Error	Error Explanation	Location of Error
"Table 1 provides an overview of the nine reports included in the meta-analysis (Hartge *et al.,* 1983; Richardson *et al.,* 1985; Whittemore *et al.,* 1988; Booth *et al.,* 1989; Harlow and Weiss *et al.,* 1989; Harlow *et al.,* 1992; Rosenblatt *et al.,* 1992; Cook *et al.,* 1997; Ness *et al.,* 2000)."	*Inaccurate reporting* Table 1 does not have the Richardson et al, 1985 study, nor do any other tables or figures in the paper. The 9th study not included in this excerpt that is in Table 1, etc., is Cramer et al, 1982.	Pg. 424; Paragraph 3; Lines 10-14
"Table 1 shows the adjusted odds ratios ranged from 0.60 (Booth *et al.,* 1989) to 3.0 (Rosenblatt *et al.,* 1992)…"	*Inaccurate reporting* In Table 1, the lowest adjusted OR is 0.60, however 0.60 is associated with Ness et al, 2000 in Table 1. Booth et al, 1989 shows an adjusted odds ratio of 0.75 in Table 1.	Pg. 425; Paragraph 1; Lines 1-2

[12] It's important to note that standard statistical packages cannot perform a meta-analysis with an invalid point estimate and 95% confidence interval; it's a fatal error that won't allow the program to run. This begs the question of how this invalid data was handled in a meta-analysis performed 'by hand.'

"…Harlow *et al.* (1992) also represents a potential problem for statistical pooling as the cases in this instance were all patients with 'borderline ovarian tumors'." "We therefore recalculated a summary relative risk without inclusion of data from the study by Ness *et al.* (2000)."	*Inaccurate reporting* Huncharek claims Harlow has issues but then removes Ness, without explanation. Also, both studies did have cases of borderline tumors, but neither had cases entirely made of borderline tumors, as the authors state.	Pg. 425; Paragraph 3; Lines 1-4 and 9-11
"All studies except that of Hartge *et al.* (1983) are full research reports with the study by Ness *et al.* (2000) published as a 'Letter to the editor'."	*Inaccurate reporting* Ness et al, 2000 is a full research paper, not a letter to the editor. Hartge, however, is a letter to the editor.	Pg. 425; Paragraph 4; Lines 1-3
Booth *et al.* (1989) 0.75 0.85–2.02	*Inaccurate reporting* Nowhere in Booth et al, 1989 is there an adjusted (or unadjusted) OR and CI listed here. Booth also does not address talc powder application to diaphragms, so this study should never have been included in the analysis.	Table 1; Booth et al, 1989
Harlow *et al.* (1992) 1.20 0.60–2.40	*Inaccurate reporting* Harlow et al, 1992 exposure category is actually Talc application via partner or applications on diaphragm, and it includes combinations with sanitary napkins or underwear. This exposure category does not belong in the meta-analysis at all.	Table 1; Harlow et al. (1992)
Harlow and Weiss, 1989 0.50 0.20–1.30	*Inaccurate reporting* Original article exposure categories include "Diaphragm storage only" and "Diaphragm storage only or with other methods". The adjusted RR and CI used in the meta-analysis is actually from "Diaphragm storage only or with other methods" and is not exclusive diaphragm exposure.	Table 1; Harlow and Weiss, 1989

‡Errors from the Huncharek 2003 Meta-Analysis are abstracted and highlighted in yellow for ease of review.

2) Lack of Replication – Diaphragm Meta-Analysis

As previously discussed, the ability to replicate research findings is pivotal to their validity and usefulness (for example, to inform programmatic and policy decisions). Utilizing the manual methods of meta-analysis described by Huncharek and colleagues in the Diaphragm Study as well as their prior 2003 paper and then utilizing standard statistical software for meta-analysis, I attempted to replicate the results reported in the Diaphragm Study. Utilizing the numbers as presented in Table 1 and Table 2 of the Huncharek 2007 Diaphragm Study (which are incorrect as detailed in Section 6.2.1 above), replication of the meta-analysis by Drs. Huncharek and Muscat according to their described methods cannot be achieved.

In their 2007 paper, Drs. Huncharek and Muscat report the following summary risk estimates for their diaphragm meta-analysis:

Adjusted Summary Risk Estimate (Table 1, 2007 Diaphragm Study): 1.03 (0.80-1.33)

Unadjusted Summary Risk Estimate (Table 2, 2007 Diaphragm Study): 1.21 (1.00-1.45)

As shown in Table 4, the pooled summary risk estimate reported in the 2007 Diaphragm Study is not replicated using the methods reported in the paper. Table 5 (and Section 6.2.3, Other Methodological Concerns, below) shows that the Huncharek 2007 Diaphragm Study deviated significantly from the stated objectives of the study, including non-talc and non-diaphragm exposures in the exposed group, and talc-exposed individuals in the "unexposed" group. A number of studies should not have been eligible for inclusion in this analysis based on the stated objectives of the study, rendering the analysis invalid.

The following conclusions can be reached from the data in Tables 4 and 5 below:

1) The adjusted summary risk estimate reported by the authors cannot be replicated utilizing their own methods and the methods referenced in their paper;

2) The crude risk estimates reported in Table 2 by the authors inappropriately include talc-exposed individuals in the control (unexposed) group, biasing the risk estimates toward no association;

3) Inclusion of talc-exposed individuals in the control group may explain the null or inverse findings observed.

The results reported by H&M in the 2007 Diaphragm Study could only be replicated by including exposed people in the denominator. This is not a valid comparison of the risk of talc exposure via

diaphragm compared to no exposure. The data are not meaningful or valid for any purpose. In order for research to be useful, it must be valid. Inaccurate and incomplete reporting of methods makes research unreliable and unusable. To revisit the author guidelines for *Cancer Medicine*:

> *Accurate and complete reporting enables readers to fully appraise research, replicate it, and use it. We expect authors to adhere to the appropriate guidelines.*

The implications of the numerous substantive errors and omissions in the 2007 Diaphragm Study are that the results do not hold up to scientific standards and are unreliable.

Table 4. Attempted replication of Huncharek 2007 Diaphragm Adjusted Meta-Analysis, Table 1+

		HUNCHAREK AND MUSCAT METHOD (manual)	GREENLAND METHOD (manual)	FIXED EFFECTS (Stata)‡
Analysis	**Studies included (n)**	**Pooled OR, 95% CI**	**Pooled OR, 95%**	**Pooled OR, 95% CI**
Diaphragm Adjusted	9	0.88 (0.42-1.34)	0.88 (0.65-1.11)	0.74 (0.55-0.93)

‡Mantel-Haenszel; The correct risk estimate and 95% CI from the Booth study was used in order for the program to run properly
+ Compare to 1.03 (0.80-1.33) as reported in Huncharek 2007

Methods Summary: Table 1 in the Huncharek 2007 Diaphragm Study reports adjusted risk estimates allegedly abstracted from the nine original studies listed in the table. Ignoring the errors described in detail in this report, meta-analytic techniques were employed in an attempt to simply replicate the adjusted summary estimate derived from the data presented in Table 1 and reported by the authors on page 424 of the Huncharek 2007 Diaphragm Study (summary OR: 1.03, 95% CI 0.80-1.33). Given the limited description of their methods, three different models were considered: (1) the inverse-variance method described by Huncharek and colleagues in their 2003 paper; (2) the method described in the Greenland 1997[13] paper Huncharek and Muscat cite for their methods (which is not the same as what they describe in their 2003 paper); and (3) the Mantel-Haenszel (M-H) fixed effects method, which is the default fixed effect method in Stata and in RevMan, used by the Cochrane Collaboration [39].

[13] In both the 2003 and 2007 Huncharek papers, the Greenland paper year is incorrectly referenced as 1996

Table 5. Attempted replication of Huncharek 2007 Diaphragm Crude Odds Ratios, Table 2+

Study	Cases	Controls	Calculated OR (Reconstructing Huncharek calculations)	Reported OR (Huncharek 2007)	Notes
Booth 1989					
Exposed	30	75	0.75	0.75	*Cannot replicate H&M; should not have been included*
Unexposed	183	343	(0.48-1.19)	(0.33-2.02)	
					95% CIs do not match; talc use via diaphragms is only estimated/assumed.
Cook 1997					
Exposed	22	35	0.92	0.96	*Cannot replicate H&M; incorrect control group*
Unexposed	206	301	(0.52-1.61)	(0.52-1.76)	
					To get close to the number reported by H&M the unexposed group includes women who had more than one type of genital talc exposure; when true unexposed group is used from original study, the OR is >1 (1.04, 95% CI: 0.59-1.85)
Cramer 1982					
Exposed	37	35	1.25	1.18	*Cannot replicate H&M; incorrect control group*
Unexposed	132	156	(0.75-2.10)	(0.59-2.35)	
					The closest estimate to what H&M report involves using data from Table 2 from the original study, which is only "potential talc exposure" vs "Talc storage among diaphragm users" as reported in Table 3 of the original study, making Table 3 the more appropriate choice. When data from Table 3 and true unexposed group is used from original study, the OR increases (1.45, 95% CI: 0.75-2.80)

Harlow 1992 Exposed Unexposed	 20 215	 21 218	 0.97 (0.51-1.83)	 0.97 (0.49-1.92)	*Cannot replicate H&M; incorrect control group* To get close to the number reported by H&M the unexposed group includes women who had other genital talc exposure; when true unexposed group is used from original study, the OR is >1 (1.14, 95% CI: 0.59-2.20)

Harlow and Weiss 1989 Exposed Unexposed	11 105	27 131	0.51 (0.24-1.07)	0.51 (0.22-1.13)	*Cannot replicate H&M; incorrect exposure group; incorrect control group; should not have been included* The closest estimate to what H&M report involves using data from the exposure category "diaphragm vs "diaphragm storage only" as reported in Table 1 of the original study, making the latter the more appropriate exposure category. In addition, the unexposed group includes women who had other genital talc exposure; when proper exposed/unexposed groups are used from original study, the OR decreases (0.41, 95% CI: 0.17-0.98). Regardless of above, exposure can include cornstarch, therefore this study should have been excluded.
Hartge 1983 Exposed Unexposed	25 106	41 127	0.73 (0.42-1.28)	0.72 (0.40-1.30)	*Cannot replicate H&M; incorrect control group* To get close to the number reported by H&M the unexposed group includes women who had other genital talc exposure; when true unexposed group is used from original study, the OR is decreases (0.60, 95% CI: 0.33-1.1).

Ness 2000 Exposed Unexposed	10 757	33 1334	0.53 (0.26-1.09)	0.53 (0.25-1.13)	*Cannot replicate H&M; incorrect control group* To get close to the number reported by H&M the unexposed group includes women who had other genital talc exposure; when true unexposed group is used from original study, the OR is increases significantly (1.53, 95% CI: 1.21-1.95).
Rosenblatt 1992 Exposed Unexposed	14 60	5 39	1.82 (0.61-5.46)	1.82 (0.55-6.34)	*Cannot replicate H&M; incorrect control group; should not have been included* To get close to the number reported by H&M the unexposed group includes women who may have had other genital talc exposure; when true unexposed group is used from original study, the OR decreases (1.40, 95% CI: 0.32-6.16). Exposure included asbestos, fiberglass, not just talc; therefore this study should not have been included.

Whittemore 1988 Exposed Unexposed	 9 179	 19 520	 1.38 (0.61-3.10)	 1.38 (0.57-3.28)	*Cannot replicate H&M; incorrect control group* To get close to the number reported by H&M the unexposed group includes women who had other genital talc exposure; when true unexposed group is used from original study, the OR increases (1.45, 95% CI: 0.63-3.35).
Methods Summary: In many cases the risk estimates reported in Table 2 of the Huncharek 2007 paper did not match crude odds ratios reported in the original studies or re-calculation of the odds ratios based upon raw frequency counts from the original studies. Therefore numbers from the original study were re-abstracted and re-analyzed in an attempt to understand the origin of the numbers presented in Table 2 of the Huncharek 2007 paper. Risk estimates and confidence intervals were calculated using medcalc.org.					

3) Other Methodological Concerns

In the 2007 Huncharek Diaphragm Study the authors convey that the objective of the paper was to address the talc-ovarian cancer research question with better precision and validity by restricting the exposure definition to a route of exposure (i.e., diaphragms) that would allegedly bring the talc in closer proximity to the target organ system:

> *The talc-ovarian cancer hypothesis could be tested with better precision and validity of the exposure to the suspected carcinogen was directly to the reproductive tract.*

In this case the "suspected carcinogen" is talc. The paper goes on to say that the purpose and methods of the study was "a meta-analysis examining the risk of developing ovarian cancer associated with the use of talc-dusted diaphragms." Despite the authors' assertions, a critical review of the paper shows that this is not the analysis that was done. Three methodological choices by the study authors undermine the internal validity of this study:

1. Including non-diaphragm exposures
2. Including non-talc exposures
3. Including subjects with talc exposure via other routes (i.e., perineal dusting) in the unexposed group

Appendix A provides a full description of the risk estimates that were included in the 2007 Diaphragm Meta-Analysis. Of the nine papers included four (44.4%) had exposure definitions that were not limited to talc-dusted diaphragms. Examples of this include:

- Harlow and Weiss, 1989 – Exposure definition included storage of diaphragm in talc or cornstarch, or included any other method of exposure (not just diaphragm)
- Rosenblatt, 1992 – Exposure definition included any fibers, including asbestos and fiberglass

A reconstruction of the analysis presented by Drs. Huncharek and Muscat in Table 2 of the Diaphragm Study demonstrates that unexposed, or control groups were constructed to include talc exposed subjects when a true unexposed control group was available, such as:

- Harlow, 1992 – Table 2 from original paper (see below) includes an unexposed category of "No genital talc application" which would be the appropriate control group; instead the authors combine all non-diaphragm talc exposures (including other genital talc exposure) and call it the control group

Table 2. History of Talc Exposure by Types of Application, Brand of Powders, Years and Frequency of Use, and Era of Use

	Cases	Controls	Adjusted OR*	95% CI
No genital talc application	121 (51.5%)	145 (60.7%)	1.0	
Any genital talc application	114 (48.5%)	94 (39.3%)	1.5	1.0–2.1
Type of application				
Only via sanitary napkins and/or underwear	9 (3.8%)	12 (5.0%)	1.1	0.4–2.8
Via partner or applications to diaphragm†	20 (8.5%)	21 (8.8%)	1.2	0.6–2.4
Via dusting powder to perineum†	85 (36.2%)	61 (25.5%)	1.7	1.1–2.7

Control (unexposed) group from original study; should have been used by Huncharek & Muscat

Exposed groups used as control (unexposed) group in 2007 Diaphragm Study

- Harlow and Weiss, 1989 – Similar to above the original paper includes an unexposed category of "No perineal exposure to powder" which would be the appropriate control group; instead the authors include other genital talc exposures in the control group

The net effect of these methodological decisions is serious and significant misclassification bias, where individuals allegedly exposed to talc via diaphragms may neither be exposed to talc nor through diaphragms. Conversely, individuals who should be unexposed are actually exposed to talc. None of these decisions represent generally accepted methodology in the field of epidemiology. The result is data that does not address the stated research question, is meaningless, and unreliable.

4) Conclusion

The premise of the 2007 Diaphragm Study - to bring increased precision to the research question of whether talc is a cause of ovarian cancer - while reasonable, was poorly executed and not realized. Drs. Huncharek and Muscat made methodological decisions that undermine their research, contrary to generally accepted practices in the field of epidemiology. These decisions significantly increased the risk of bias in the study thereby confusing, rather than clarifying, the research question. Ultimately, Huncharek and colleagues present an analysis that is flawed, invalidated by errors in fact and methodology, and lack of transparency. The implications of the

numerous substantive errors and omissions in the 2007 Diaphragm Study is that the results do not hold up to scientific standards and are unreliable.

6.3 PCPC 2009 RESPONSE TO CITIZEN'S PETITION TO THE FDA

The 2009 H&M report submitted to FDA relied heavily on Huncharek and Muscat's own prior studies and conclusions from their 2003 and 2007 papers. A review of the FDA website shows that the 2009 H&M Report was the only commentary that was received in response to the Citizen's Petition filed by Dr. Epstein.

The opinions and conclusions of Drs. Huncharek and Muscat represented in the 2009 report were subsequently published in 2011 for the medical and scientific community. The report was submitted in 2009 to the FDA as evidence of the PCPC's position that "the available ovarian cancer epidemiology studies do not support a causative role for talc" based on: (1) lack of a clear dose-response relationship, (2) uncontrolled confounding and (3) selection bias. FDA's denial of the Citizen's petition (April 1, 2014) cites directly to these positions as the basis, in part, for their denial.[14]

1) Dose-Response Analysis

One of the primary reasons that Huncharek and Muscat dismiss the positive and statistically significant associations consistently observed in the evidence base is their assertions that (1) a linear dose-response is required for a causal relationship and (2) any observation of an inverse dose-response relationship automatically supports a non-causal conclusion. Drs. Huncharek and Muscat rely primarily on data from their 2003 paper to support this position, in particular Table II from the 2003 Huncharek Meta-Analysis, which is discussed in detail in Section 6.1 of this report. This 2003 table—including all of the incorrect data contained therein—was republished as Table 3 in their 2011 publication.

As discussed previously, the results and conclusions of their own dose-response analysis in the 2003 Huncharek Meta-Analysis are invalid and unreliable. Beyond this H&M misrepresent the other available data on dose response.

There is evidence of a positive dose-response in the epidemiological studies on talc and ovarian cancer. Table 6 below provides two examples of how the authors overlooked evidence of a dose-

[14] Huncharek and Muscat also assert that there was no biologic plusability for Talcum Powder products as asbestos had been "eliminated" from them such products since the 1970's. I have not been asked to address this but I have been informed that there is evidence that asbestos has been found in talc products since the 1970's.

response. In the case of the Chang 1997 paper, the study authors' own findings and conclusions are misrepresented.

Table 6. Unacknowledged Positive Dose Response Data

Author, Year	Huncharek and Muscat's Comments	Original Author Comments
Chang, 1997	They acknowledged that the lack of a dose-response needs clarification. In fact, an inverse dose-response is suggested by the data in Table 2 of the manuscript. [8(p12)]	A questionable dose-response relationship was observed between duration or frequency of exposure and risk. Duration as a continuous variable indicated that **risk may increase with increasing years of talc exposure.** [3(p2400)]
Harlow, 1992	* Huncharek and Muscat provide no discussion of Harlow 1992 in the PCPC Report nor is the paper listed in the bibliography.	When monthly frequency was considered as a continuous variable in the logistic model the chi-square linear test of trend was 4.06 (p=0.046), indicating that the **risk for ovarian cancer increased significantly with increasing frequency of applications per month.** [27(p22)]

Even if there was no evidence of a dose-response: 1) It is not required for inferring causation according to generally accepted scientific methods, and 2) there are many reasons why a *linear* dose response curve may not be observed in individual epidemiological studies. Examples include a non-monotonic dose-response relationship and reducing a quantitative variable to arbitrary categories, which can obscure a dose-response relationship. The authors do not report the positive dose-response data described in the individual epidemiological studies and do not offer a discussion of the reasons why a dose-response relationship may be obscured even when the association is causal, presenting only data which supports their conclusion. Huncharek and Muscat's assertions on dose-response are based on the propagation of an error-filled analysis along with an inaccurate and incomplete review of the available evidence.

2) Contradictory and Unsupported Claims of Uncontrolled Confounding

Epidemiologists are tasked with evaluating the potential for uncontrolled confounding to bias the risk estimates of a study or an evidence base. Either uncontrolled confounding is a concern and risk estimates should be adjusted to the extent possible to address it, or uncontrolled confounding is not a concern and the crude risk estimates represent the best estimate of risk. The authors are inconsistent in their treatment of confounding.

Beginning in 2003 and continuing through the 2009 report, Drs. Huncharek and Muscat claim that uncontrolled confounding can explain the consistently positive associations observed in the epidemiological studies.

If this is their belief, the generally accepted scientific methods for analysis of the evidence base would look at risk estimates that have been adjusted for potential confounders (See Section 4.1, Confounding). However, on page 9 of the 2009 H&M Report, Huncharek and Muscat state that:

> *The meta-analysis by Huncharek et al. included the adjusted odds ratio, but in retrospect* ***the lower crude OR was probably the better measure*** *when pooling the results. (Emphasis added)*

This position is echoed in Muscat's deposition when he stated:

> *The Huncharek analysis is an unadjusted confidence interval…and it's correct. That's the way you do the meta-analysis. (p.475 Muscat Deposition).*

These positions are contradictory and are not explained. If uncontrolled confounding is a bias explaining consistently positive associations, there is no scientific reason to hold up a crude, or unadjusted, risk estimate (meaning no control for confounding factors) as the best estimate of the risk of ovarian cancer from talc exposure.

On page 4 of the 2009 H&M Report, Drs. Huncharek and Muscat introduce smoking as a specific confounder that could "produce a spurious positive finding." They further discuss this on page 23, where they cite an article by Rosenblatt and colleagues as empirical data supporting their assertion that smoking is an important confounder. In order to be a strong confounder, smoking would have to be strongly associated with talc use and ovarian cancer. The data the authors cite to support the talc-smoking relationship is in Table 1 of Rosenblatt *et al*., showing an odds ratio of 1.2 (95% CI: 1.0, 1.6))[15], meaning that in their study smokers were 1.2-times more likely to report powder exposure of any type of application. This finding is not statistically significant at the alpha level of 0.05, as it includes the null value of 1.0 in the 95% confidence interval. Despite this being a "weak" association by their own definition [8], Huncharek and Muscat claim a positive significant association from the Rosenblatt data for a relative risk of 1.2 that is non-statistically significant. However, in other sections of the report it is claimed that "weak" associations are highly susceptible to bias and are unreliable.

> *The weak association shown in a sub-set of observational studies can potentially be explained by numerous alternative hypotheses (Huncharek 2009, p. 30).*

> *Measures of association of this magnitude are often difficult to interpret (Huncharek 2009, p. 26).*

[15] There appears to be an error in the Rosenblatt 1998 paper. The authors report in their Table 1 an OR of 1.2 (1.0, 1.6) for smoking but replace that in the narrative with an OR of 1.3 (1.0, 1.8). This is being noted for accuracy but does not change the point that Huncharek and Muscat relied upon this number to support their position that smoking is a confounder of the talc-ovarian cancer relationship.

Generally accepted scientific methods do not allow similar "weak" associations unsupportive of a position to be treated differently than "weak" risk estimates supporting a position.

A similar position is taken by the authors with regard to statistical significance, citing lack of statistical significance to discount the validity of risk estimates unsupportive of their opinions and overlooking it, when it is supportive. As noted above, the authors rely on non-statistically significant data from Rosenblatt 1998 to support the position that smoking is an important confounder, while simultaneously discounting findings that similarly do not achieve statistical significance that are unsupportive of their positions. As example, on page 20 of the 2009 H&M Report, the authors claim the findings of their subgroup meta-analysis of hospital-based controls "showed no increased risk," when it actually showed a 19% increased risk of ovarian cancer for talc-exposed patients. Promoting a risk estimate as meaningful when it supports a position (RR=1.20; 1.0-1.6, smoking and talc use from Rosenblatt 1998) and disregarding a nearly identical risk estimate when it does not support a position (OR=1.19; 0.99-1.41, talc exposure and ovarian cancer, Huncharek 2003) is not generally scientifically accepted.

3) Analysis of Selection Bias

Drs. Huncharek and Muscat re-assert in the 2009 PCPC Report a position that they introduce in their 2003 Meta-Analysis: selection bias in the population based case-control studies may be resulting in a false positive association. The data they offer to support this assertion is their own, inaccurate data from the 2003 Meta-Analysis wherein their subgroup analysis showed a lower summary risk estimate for hospital based case-control studies compared to population-based case control studies. This analysis contains multiple substantial errors and cannot be replicated. Setting aside the significant errors, this assertion is entirely unsupported, which the authors admit [8(p16)].

Further, the authors repeatedly discuss the observed differences between hospital and population-based case control studies without acknowledging the intrinsic, well-documented bias in hospital-based case control studies that would actually serve to underestimate the true risk. Unfortunately, the authors unevenly discuss the evidence base, only citing studies that support the case for a non-causal relationship and utilizing the observed difference in risk estimates between population and hospital-based case-control studies as evidence undermining a causal association, without considering and discussing other more scientifically accepted explanations for the observed difference – including the implications of their theory of a "treatment effect."

As before, Huncharek and Muscat's conclusions on this issue depend on error-filled analyses and unsubstantiated claims that are invalid.

4) Other Methodological Concerns

In addition to the flawed analyses and conclusions that were repeatedly asserted and disseminated to the FDA and the medical and scientific community, Huncharek and Muscat's review of the

epidemiological literature in the 2009 H&M report is questionable based on misrepresentation of the epidemiological evidence base and departure from generally accepted scientific standards.

Huncharek and Muscat confuse and misuse basic epidemiological concepts

Association versus causation. Association and causation are not equivalent. Association is a statistical relationship between two variables; an association may be detected by conducting a range of statistical tests. Causation involves an evaluation as to whether an observed statistical association represents a cause-effect relationship and requires inferences beyond the data from a single study. An observed statistical association between an exposure and a disease does not automatically infer a causal relationship and, conversely, the absence of an association does not necessarily imply the absence of a causal relationship. Drs. Huncharek and Muscat confuse these two distinct epidemiological concepts. This is most apparent in the 2003 paper in which they make causal judgments based on the results of their meta-analysis.

> *In summary, pooling data from the sixteen available observational studies examining the relationship between perineal use of cosmetic talc and the development of invasive epithelial ovarian cancer failed to show evidence of a causal relationship (p 1960).*

On page 19 of the PCPC report, Huncharek and Muscat state (in reference to Epstein et al.'s analysis of their own 2003 meta-analysis):

> *Epstein et al. note, "An analysis of 16 pooled studies confirmed a statistically significant 33% increased risk of ovarian cancer associated with the perineal use of talc." Essentially, the petitioners erroneously indicate that the meta-analysis supports an association between perineal talc dusting and ovarian cancer risk."*

This statement is incorrect and the statement of fact by the Epstein authors is correct. As reported in the 2003 meta-analysis by Huncharek and Muscat, the results of the primary meta-analysis do in fact demonstrate a 33% increased risk of ovarian cancer and the finding is also statistically significant. Claiming that such data do not demonstrate an association is not generally scientifically accepted.

Causation cannot be inferred or discounted based on a single study. Epidemiology as a practice utilizes evidence provided from a multitude of disciplines in order to assess causation and recognizes that it is the collective weight of evidence that drives its recommendations.[40] Despite this, the authors repeatedly make causation assertions that are not generally scientifically accepted. As example, on page 9 of the PCPC report they state in reference to the Purdie 1995 paper:

> *The association with talc cannot be considered causal in this individual study as the exposure is crudely defined, the findings based on the whole dataset are marginally significant, and there are no dose-response data.*

Their evaluation of this individual study fails to align with generally accepted methods and makes an unsupported leap to causation. A causal analysis cannot be determined based on a single piece of evidence but requires consideration of the totality of relevant evidence.

Association versus statistical significance. Huncharek and Muscat also repeatedly confuse the concepts of association and statistical significance.

On page 7 of the PCPC report Huncharek and Muscat:

> *Two meta-analyses by Huncharek et al. (2003) and Langseth et al. (2008) both show significant differences in summary odds ratios between population-based and hospital-based case control studies, with the latter showing generally null results.*

That statement is false. The results of their subgroup analysis showed a 19% increased risk of ovarian cancer for talc-exposed individuals versus unexposed (OR 1.19, 95% CI: 0.99-1.41). Because the number of studies was small the precision of the estimate was reduced and the 95% confidence interval included the null value, which is a reflection of statistical hypothesis testing and not the magnitude or direction of the association. Given a valid analysis, the point estimate is always the most likely value of the true population parameter and shows a positive association (i.e., increased risk) for both population-based and hospital-based case control studies in both the Huncharek 2003 and Langseth 2008 analyses.

The use of inappropriate terminology and misrepresentation of data is scientifically misleading. Huncharek and Muscat misused and conflated important epidemiological concepts. Their analyses and resulting conclusions repeatedly fall short of generally accepted methods and scientific standards.

Contradictory positions on key methodological issues

Objective presentation of data and findings is a key tenet of scientific research standards: "Presented data must represent the findings in an unbiased, accurate and transparent manner."[16] According to the American College of Epidemiology[17]:

> *It is incumbent upon epidemiologists (as members of the broader scientific community) to ensure that objectivity prevails at every step of the research process. Partiality can arise through a scientist's own biases and preconceived notions about a problem being investigated. Maintaining honesty and impartiality in the design, conduct, interpretation, and reporting of research findings is essential. Truth-telling and objectivity are professional duties and they can also be thought of as virtues.*

[16] Instructions to Authors, *Cancer Medicine*
[17] https://www.acepidemiology.org/ethics-guidelines

When evaluating evidence surrounding a research question (like "Does talc cause ovarian cancer?"), key methodological questions and approaches will arise and a scientifically objective position should be asserted from the outset. Contrary to this, Huncharek and Muscat vacillate between important methodological positions on these questions. I discuss some of these in detail below.

Is control for confounding important or not? As discussed previously, as part of an evaluation of a research question, in this case 'does talc cause ovarian cancer,' an epidemiologist must evaluate whether and to what extent the inability to control for confounding factors could (1) result in a biased risk estimate and (2) change the conclusions.

On page 9 of the PCPC report, Huncharek and Muscat state:

> *The meta-analysis by Huncharek et al. included the adjusted odds ratio, but in retrospect* ***the lower crude OR was probably the better measure*** *when pooling the results. (Emphasis added)*

This statement advocates for risk estimates that are unadjusted (meaning no control for confounding factors) as the best estimates of the risk of ovarian cancer from talc exposure. This position is echoed in Muscat's deposition when he states:

> *The Huncharek analysis is an unadjusted confidence interval…and it's correct. That's the way you do the meta-analysis. (p. 475 Muscat Deposition).*

However, contrary to these two statements, the authors repeatedly express concern that uncontrolled confounding may be resulting in biased risk estimates. As example on page 7 of the PCPC report, Huncharek and Muscat state:

> *Huncharek et al. (2003, 2007) suggest multiple sources of bias that could produce a spurious positive finding, including unaccounted effects of cancer treatment and confounding by smoking.*

The two positions cannot be held simultaneously.

Are modest relative risks reliable? Throughout this and prior reports the authors repeatedly cite the "weak" association between talc and ovarian cancer as being intrinsically at risk of bias just by nature of being a relative risk less than two.

On page 7 of the PCPC report, Huncharek and Muscat state:

> *Given the lack of supporting evidence from in vivo and clinical research studies using human subjects, the weak and inconsistent epidemiological associations, that also lack a gradient in effect, argues against a claim of causality.*

The authors assert that "weak" associations are intrinsically susceptible to bias. Any risk estimate, regardless of size, must be critically analyzed for risk of bias within the context of specific study methodology. A risk estimate of 1.30 can be highly reliable based on a review of the underlying study or at high likelihood of bias based on a review of the underlying study. More modest, or "weak," risk estimates can be causal and there are numerous examples of this in the field of epidemiology such as the benefits of fruit and vegetable intake and the risks from UV radiation[18]. One cannot just look at a risk estimate in the absence of a thorough review of the underlying study methodology and claim bias.

Despite repeatedly claiming that "weak" risk estimates are highly susceptible to bias and are unreliable, Huncharek and Muscat rely on a "weak" risk estimate when it suits their position. On page 26 of the 2009 H&M Report they cite the Rosenblatt 1998 paper as supportive of their position that smoking as "an example of a factor that could confound the weak effect shown for perineal talc" and ovarian cancer:

> *Since Rosenblatt et al. reported that smokers are more likely to engage in perineal talc dusting compare with non-smokers, an imbalance in smokers across cases and control groups in epidemiological studies of the talc/ovarian cancer association could contribute to a spurious positive association (Rosenblatt, 1998).*

As discussed previously, Huncharek and Muscat claim a positive significant association from the Rosenblatt data for a relative risk of 1.2 that is non-statistically significant, despite their earlier assertions that "weak" estimates are unreliable.

Either a relative risk that is "weak" and non-statistically significant can be meaningful and contribute to a body of evidence or it is not because it is intrinsically biased (according to the Huncharek and Muscat). It cannot be meaningful when it supports your position and weak when it does not.

Is statistical significance required or is it not? Similar to their contradictory positions on the strength of the association, Huncharek and Muscat flip-flop on the importance of statistical significance in interpreting epidemiological risk estimates. As noted above, they rely on non-statistically significant data from Rosenblatt 1998 to support their position that smoking is a confounder but discount findings that do not achieve statistical significance when it opposes their position. One of the most significant examples of this is the findings from their subgroup meta-analyses looking at hospital versus population-based controls. On page 20 of the PCPC report, Huncharek and Muscat state:

[18] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5837313/pdf/dyw319.pdf
http://www.beauty-review.nl/wp-content/uploads/2014/06/Meta-analysis-of-risk-factors-for-cutaneous-melanoma-II.-Sun-exposure.pdf

> *Studies using hospital derived controls showed no increased risk while those employing population-based controls were consistent with a 38% increased risk of disease.*

This statement is inaccurate, as the summary relative risk estimate for hospital based studies was 1.19 in their analysis – representing a 19% increased risk of ovarian cancer for talc-exposed patients. The fact that the 95% confidence interval includes the null value of 1.0 (0.99-1.41) speaks only to the question of statistical significance testing, not the strength or magnitude of the association. The authors validate such a risk estimate when it supports their position (RR=1.20; 1.0-1.6, smoking and talc use from Rosenblatt 1998) and discount the nearly identical risk estimate when it does not support their position (OR=1.19; 0.99-1.41), talc exposure and ovarian cancer from Huncharek 2003).

Are the data consistent? Consistency according to Bradford Hill is generally described as the situation in which the association has been "repeatedly observed by different persons, in different places, circumstances and times" [42]. The guidelines do not put any constraints on how precisely consistency is measured. Meta-analysis is a statistical tool that helps us measure consistency of findings across an evidence base. As discussed previously, there are measures that are calculated and reported routinely as part of meta-analyses that speak to consistency: measures of heterogeneity (i.e., Q statistic, I^2). These statistical tests of heterogeneity are routinely used to make decisions about the appropriate methods for combining studies and for concluding consistency or inconsistency of findings [22].

On page 26 of the PCPC Report, Huncharek and Muscat claim that the epidemiological evidence base is not consistent:

> *Consistency of an effect could contribute to a causal claim despite a finding of a weak association…Despite the claims of the petitioners, a review of available evidence shows that the epidemiological evidence is NOT consistent across studies or across study types.*

This statement is directly contrary to their own results from their 2003 meta-analysis and contradicts their own words in the 2003 paper in which they found the evidence base to be consistent enough for pooling in a meta-analysis:

> *Analysis for heterogeneity demonstrated that the data were homogenous (p= 0.17) and could be combined in a meta-analysis.*

5) Conclusion

In their 2009 H&M Report to the FDA in opposition to a mandatory warning on talcum powder products that was requested by CPC and Dr. Epstein, and in their subsequent 2011 publication, Drs. Huncharek and Muscat rely heavily upon their own flawed 2003 and 2007 meta-analyses to dismiss the consistently observed positive association between talc and ovarian cancer. They fall short of key research standards, including but not limited to transparency and accuracy. As a

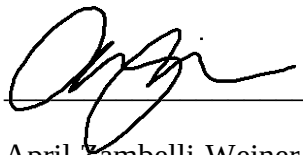
result, the causal analysis and conclusions presented by Drs. Huncharek and Muscat in their 2009 report are invalid.

7 Conclusion

I was tasked with evaluating the scientific rigor and validity of the research, analyses, conclusions and opinions produced by Drs. Huncharek and Muscat beginning in 2003 and ending in 2011. Their analyses were presented to FDA to effect important policy and regulatory decisions, regarding talc exposure and the risk of ovarian cancer.

In conducting my evaluation, I have applied generally accepted principles of epidemiology and biostatistics. My application of these methods to a critical assessment of these manuscripts and report leads to my conclusion and opinion that key analyses – which were repeatedly referenced and reproduced in the scientific literature and in submission to the FDA over the course of almost a decade – contained numerous substantive errors. The number of errors, from simple abstraction of the underlying data, failure to follow their own described methods, inappropriate methodological decisions, lack of replication, and reliance on uncontrolled confounding make these studies and the derived 2009 FDA report inaccurate. Any conclusions reached on dose-response, uncontrolled confounding or selection bias that relied upon or were influenced by data, analyses, opinions or conclusions presented within these studies and report, are at high risk of bias. I hold this opinion and all opinions set forth in this report to a reasonable degree of scientific certainty.

By



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9 Appendix A – Exposure Definitions Used in Huncharek 2007 Diaphragm Study, Adjusted Risk Estimates

In the 2007 Diaphragm Study Huncharek and colleagues describe in their methods that they derived risk estimates that: "reflect the risk of developing ovarian cancer associated with the practice of dusting contraceptive diaphragms with cosmetic talc." A review of the actual exposure definitions included in their analysis demonstrates the following: **The majority of risk estimates used in their meta-analysis did not address the stated research question, that is isolating the risk of ovarian cancer associated with talc-diaphragm exposure versus non-talc exposure.**

Study	Adjusted OR (95% CI) reported in Huncharek et al, 2007, Table 1	Exposure Definition in Original Article
Booth, 1989	0.75 (0.85-2.02) [a]	Monthly genital use ✓ Not specifically diaphragm use ✓ Reported OR and 95% CI used in the Huncharek paper cannot be found anywhere in the original Booth article)
Cook, 1997	0.80 (0.40-1.40)	Diaphragm storage - exclusive
Cramer, 1982	1.56 (0.62-3.88)	All/any diaphragm storage in talc ✓ Can include any duration of use ✓ Not exclusively diaphragm use (meaning individuals could have other sources or routes of exposure; model not adjusted for this)
Harlow, 1992	1.20 (0.60-2.40)	Partner or applications to diaphragm[b] ✓ Not exclusively diaphragm use ✓ Can also include "combinations with sanitary napkins or underwear"
Harlow and Weiss, 1989	0.50 (0.20-1.30)	Diaphragm storage in talc OR cornstarch only or with other methods of exposure ✓ Exposure can include cornstarch ✓ Not exclusively diaphragm use, category could include other routes of exposures
Hartge, 1983	0.80 (0.40-1.40)	Diaphragm in talc
Ness, 2000	0.60 (0.30-1.20)	Diaphragm/Cerv Cap[c] ✓ Not exclusively diaphragm use, may include other routes of exposure
Rosenblatt, 1992	3.0 (0.80-10.8)	Diaphragm ✓ Exposure included asbestos, fiberglass, and talc
Whittemore, 1988	1.5 (0.63-3.58)	Diaphragm only - exclusive

[a] This study does not contain any ORs for diaphragm storage in talc powder. See error list document.
[b] Includes combinations with sanitary napkins or underwear.
[c] Subjects may have used talc on more than one area of the body

10 Appendix B. Dose Response Data from 2003 Huncharek Meta-Analysis, Adjusted v. Unadjusted

	Years of Talc Use				# Talc Applications per Month			
Author	**Exposure Category**	**Adjusted OR (95% CI) ‡**	**Unadjusted OR (95% CI)**	**Huncharek OR (95% CI)**	**Exposure Category**	**Adjusted OR (95% CI) ‡**	**Unadjusted OR (95% CI)**	**Huncharek OR (95% CI)**
Booth, 1989	NG				1x*	0.7 (0.3-1.8)	0.68 (0.28-1.65)	0.7 (0.3-1.8)
					4x	2.0 (1.3-3.4)	1.73 (1.12-2.68)	2.0 (1.3-3.4)
					30x	1.3 (0.8-1.9)	1.20 (0.81-1.77)	1.3 (0.8-1.9)
Chang, 1997	<30	1.697 (1.09-2.64)	1.62 (1.11-2.50)	1.7 (1.09-2.68)	<10	1.836 (1.24-2.73)	1.86 (1.27-2.70)	1.84 (1.24-2.73)
	30-40	1.435 (0.96-2.15)	1.53 (1.05-2.21)	1.44 (0.96-2.15)	10-25	1.128 (0.74-1.72)	1.22 (0.82-1.81)	1.13 (0.74-1.72)
	>40	0.865 (0.54-1.38)	0.92 (0.60-1.41)	0.96 (0.54-1.38)	>25	0.951 (0.61-1.49)	0.98 (0.64-1.51)	0.95 (0.61-1.49)
Cook, 1997	0-5.5**	1.8 (0.9-3.5)	1.51 (0.80-2.86)	1.8 (0.9-3.5)	NG			
	5.5-13.5	1.6 (0.9-2.9)	1.53 (0.85-2.77)	1.6 (0.9-2.9)				
	13.5-27	1.2 (0.6-2.4)	1.59 (0.84-2.98)	1.2 (0.6-3.4)				
	>27	1.8 (0.9-3.4)	2.74 (1.45-5.17)	1.8 (0.9-3.4)				
Cramer, 1999	<20	1.86 (1.16-3.00)	1.85 (1.17-2.92)	1.9 (1.2-3.0)	<30	2.21 (1.37-3.56)	2.38 (1.50-3.79)	2.2 (1.4-3.6)
	20-30	1.33 (0.76-2.30)	1.28 (0.75-2.19)	1.3 (0.8-2.3)	30-39	1.17 (0.78-1.76)	1.20 (0.81-1.79)	1.2 (0.8-1.8)
	>30	1.44 (0.91-2.26)	1.66 (1.08-2.56)	1.4 (0.9-2.3)	40+	1.57 (0.80-3.10)	1.60 (0.82-3.10)	1.6 (0.8-3.1)
Gertig, 2000	NG				4-24 ***	0.99 (0.67-1.46)	0.93 (0.63-1.37)	0.99 (0.67-1.46)
					>/=30	1.12 (0.82-1.55)	1.10 (0.80-1.52)	1.12 (0.82-1.55)
Harlow, 1992	<10	1.2 (0.5-2.6)	1.12 (0.52-2.41)	1.2 (0.5-2.6)	<5	1.5 (0.8-2.7)	1.37 (0.78-2.40)	1.5 (0.8-2.7)
	10-29	1.6 (1.0-2.7)	1.51 (0.93-2.45)	1.6 (1.0-2.7)	5-29	1.2 (0.6-2.2)	1.15 (0.63-2.12)	1.2 (0.6-2.2)
	>=30	1.6 (1.0-2.7)	1.53 (0.95-2.47)	1.6 (1.0-2.7)	>=30	1.8 (1.1-3.0)	1.70 (1.06-2.70)	1.8 (1.1-3.0)
Ness, 2000	<1	2.0 (1.0-4.0)	2.04 (1.03-4.04)	2.0 (1.0-4.0)	NG			
	1-4	1.6 (1.1-2.3)	1.54 (1.12-2.12)	1.6 (1.1-2.3)				
	5-9	1.2 (0.8-1.9)	1.38 (0.91-2.11)	1.2 (0.8-1.9)				
	10+	1.2 (1.0-1.5)	1.28 (1.05-1.57)	1.2 (1.0-1.5)				
Whittemore, 1988	1-9	1.60 (1.00-2.57)	1.47 (0.92-2.33)	1.60 (1.00-2.57)	1-20	1.27 (0.82-1.96)	1.16 (0.76-1.77)	1.27 (0.82-1.96)
	10+	1.11 (0.74-1.65)	1.06 (0.72-1.56)	1.11 (0.74-1.65)	20+	1.45 (0.94-2.22)	1.40 (0.92-2.13)	1.45 (0.94-2.22)
Wong, 1999	1-9	0.9 (0.6-1.5)	1.01 (0.66-1.56)	0.9 (0.6-1.5)	NG			
	10-19	1.4 (0.9-2.2)	1.55 (1.01-2.38)	1.4 (0.9-2.2)				
	>=20	0.9 (0.6-1.2)	0.99 (0.74-1.34)	0.9 (0.6-1.2)				

NG=Not Given; Numbers in red represent values used in the 2003 Huncharek Meta-Analysis do not match either the adjusted or unadjusted values from the original epidemiological studies

‡ Values were abstracted from the original articles

* Booth categorizes as Monthly Weekly, and Daily. There is also another category, "Never", which Huncharek did not include.

** Cook categorizes as <=2,000 days, 2,001-5,000 days, 5,001-10,000 days, and >10,000 days.

*** Gertig reports as 1-6/wk and Daily. There is also a category, "<1/wk" which Huncharek did not include.

11 Appendix C. Curriculum Vitae for April Zambelli-Weiner, Ph.D.

Curriculum Vitae

April Zambelli-Weiner, Ph.D., M.P.H.

Address 1231 Tech Ct, Suite 201 | Westminster, MD 21157
Email aweiner@tti-research.com
Telephone (800) 580-2990, ext. 101 **Fax** (888) 391-5380

Current Professional Affiliations

2011- Present Founder, President, Principal Epidemiologist
TTi Health Research & Economics, Westminster, MD

Positions Held

2003-2011 Principal Epidemiologist
Epidemiology International, Inc.
Hunt Valley, MD

2000- 2003 Data Analyst and Manager, Data Analysis Core Facility
The Johns Hopkins Asthma and Allergy Center, Division of Clinical Immunology, Baltimore, MD

1997-1999 Research Assistant
Washington University School of Medicine, Division of Internal Medicine, Department of Gastroenterology, St. Louis, MO

Education

Post-Doc Clinical Immunology
Johns Hopkins University School of Medicine, Baltimore, MD

PhD Epidemiology / Human Genetics
Johns Hopkins University School of Public Health, Baltimore, MD

MPH Epidemiology
Saint Louis University School of Public Health, St. Louis MO

BA Chemistry and English
Washington & Jefferson College, Washington, PA

Key Skills & Expertise

- Extensive experience in public health and health care research including collection of scientific and health data from various sources, including both primary and secondary data sources; compilation of gathered data in appropriate formats
- Employing advanced statistical techniques in the analysis of epidemiological, clinical, lifestyle, risk factor, and environmental data
- Designing and implementing epidemiological data collection instruments and systems
- Exceptional analytical skills, with the capacity to process scientific and medical data
- Proficiency in manipulating and analyzing large, complex datasets
- Proficiency in statistical tools including Stata, SPSS, SQL, advanced Excel, among other more specialized applications
- Capability to classify data issues, present problems, and implement solutions
- Familiarity with public health, health care, and socio-demographic data sources
- Analyzing incidence and prevalence rates of disease according to subgroups and risk factors
- Development of analytic strategies and statistical analysis plans
- Conducting literature reviews and weight of evidence analyses
- Understanding of and experience implementing laboratory and clinical protocols
- Knowledge of and experience with a wide range of cellular and molecular methodologies utilized in *in vitro* and *in vivo* studies
- Excellent written and verbal communication skills; proven ability to interface with stakeholders and resolve doubts, queries and issues related to study design, data collection or integrity, and statistical analyses
- Exceptional ability to summarize and present results clearly and concisely, including preparation of models, charts, tables, pie diagrams, and graphics to present scientific data in easy to understand formats
- Expert in communicating research goals, approach, results, and implications to a broad array of clients and stakeholders, including governmental agencies, corporate management teams, academic faculty, the legal profession, and the lay public
- Project Management, including top-level oversight of complex, multi-site research studies
- Strategic planning, needs assessment, and program design

Memberships and Appointments

American College of Epidemiology
American Public Health Association
International Society for Pharmacoepidemiology
International Society for Pharmacoeconomics and Outcomes Research
International Society for Environmental Epidemiology
Maryland Public Health Association

Patents

"Antimicrobial Compositions" Publication Number: 20120121723, Publication date: 05/17/2012

"Antimicrobial compositions" Publication Number: 20090312279, Publication date: 12/17/2009

"Antimicrobial compositions" Publication Number: 20080194518, Publication date: 08/14/2008

"Antimicrobial compositions" Publication Number: 20070258996, Publication date: 11/08/2007

Peer Review

Reviewer for *Birth Defects Research*
Reviewer for *Journal of Women's Health*
Reviewer for National Eye Institute (NIH)

Selected Federal Research Support

Years Funded	Funding Organization	Project Title	Role
Jan 2018-Present	CDC	National Study to Explore Early Development (SEED) [National Center for Birth Defects and Developmental Disabilities]	Senior Advisor, Epidemiology
2017-Present	CDC	Rigorous Evaluation of Health Equity Strategies to Address Heart Disease and Stroke Prevention [National Center for Chronic Disease Prevention and Health Promotion]	Senior Subject Matter Expert, Epidemiology
2015-2017	CDC	Assess the Cost-Effectiveness of Hypertension Management Strategies in Persons with Chronic Kidney Disease [National Center for Chronic Disease Prevention and Health Promotion]	Senior Epidemiologist
2016	CDC	Qualitative Evaluation of the CDC's Prevention Research Center Program Network [National Center for Chronic Disease Prevention and Health Promotion]	Senior Advisor
2015-2016	CDC	Design and Preparation for a National Study of the Prevalence of Female Genital Mutilation/Cutting (FGM/C) in the United States [National Center for Chronic Disease Prevention and Health Promotion]	Project Director
2011-2012	NIH	Comprehensive Needs Assessment of the Hazardous Substance Databank	Project Director
2009-2010	CDC	Evaluation of National Surveillance Systems: Detection and Monitoring of Disparities in Vision Health and Disability [National Center for Chronic Disease Prevention and Health Promotion]	Epidemiologist Lead

Publications

Journal Articles

Klein AP, Kovac I, Sorant AJM, Baffoe-Bonnie A, Doan BQ, Ibay G, Lockwood E, Mandal D, Santhosh L, Weissbecker K, Woo J, **Zambelli-Weiner A**, Zhang J, Naiman DQ, Malley J, Bailey-Wilson JE. " Importance Sampling Method of Correction for Multiple Testing in Affected Sib-pair Linkage Analysis." BMC Genet. 2003 Dec 31;4 Suppl 1:S73.

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Feb 15;171(4):361-70

Zambelli-Weiner A, Ehrlich E, Stockton ML, Grant AV, Zhang S, Levett PN, Beaty TH, Barnes KC. "Evaluation of the CD14/-260 polymorphism and house dust endotoxin exposure in
the Barbados Asthma Genetics Study." J Allergy Clin Immunol. 2005 Jun;115(6):1203-9.

Barnes KC, Grant AV, Baltadzhieva D, Zhang S, Berg T, Shao L, **Zambelli-Weiner A**, Anderson W, Nelsen A, Pillai S, Yarnall DP, Dienger K, Ingersoll RG, Scott AF, Fallin MD, Mathias RA, Beaty TH, Garcia JG, Wills-Karp M. "Variants in the gene encoding C3 are associated with asthma and related phenotypes among African Caribbean families." Genes Immun. 2006 Jan;7(1):27-35.

Barnes KC, Grant A, Gao P, Baltadjieva D, Berg T, Chi P, Zhang S, **Zambelli-Weiner A**, Ehrlich E, Zardkoohi O, Brummet ME, Stockton M, Watkins T, Gao L, Gittens M, Wills-Karp M, Cheadle C, Beck LA, Beaty TH, Becker KG, Garcia JG, Mathias RA. "Polymorphisms in the novel gene acyloxyacyl hydroxylase (AOAH) are associated with asthma and associated phenotypes." J Allergy Clin Immunol. 2006 Jul;118(1):70-77.

Arnold JW, deLaubenfels E, **Zambelli-Weiner A**. "Quantitative assessment of hard surface disinfection activity against the food-borne pathogen, *Listeria monocytogenes*." The Journal of AOAC International. 2006 Nov-Dec;89(6):1617-21.

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Zambelli-Weiner A, Crews JE, Friedman DS. Building a Basis for Action: Enhancing Public Health Surveillance of Visual Impairment and Eye Health in the US. *American Journal of Ophthalmology*. 2012 Dec;154(6 Suppl):S8-S22.

Harness JK, Davies K, Via C, Brooks E, **Zambelli-Weiner A**, Shah C, Vincini F. Meta-Analysis of Local Recurrence of Invasive Breast Cancer after Electron Intraoperative Radiotherapy. *Annals of Surgical Oncology* (2018): 1-11.

Zambelli-Weiner A, Via C, Yuen M, Weiner DJ, Kirby RS. First Trimester Ondansetron Exposure and Risk of Structural Birth Defects. *Reproductive Toxicology* (2018).

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Posters and Presentations

Kirby RS**, Zambelli-Weiner A**, Via C, , Yuen M, Weiner D. Early Pregnancy Ondansetron Exposure and Risk of Structural Birth Defects, Platform presentation,
58th Teratology Society Annual Meeting, 2018, Clearwater, Florida.

Zambelli-Weiner A, Via C, Kirby RS, Yuen M, Weiner D. Early Pregnancy ondansetron exposure is associated with increased risk of structural birth defects in offspring in a large, US population sample. Poster presentation, 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International Conference, Baltimore, MD.*Semi-Finalist for Research Poster Presentation Award.

Zambelli-Weiner A, Via C, Yuen M, Weiner D. Evaluating the relationship between in-utero methylprednisolone exposure and birth defects. Poster presentation, 2018 International Society

for Pharmacoeconomics and Outcomes Research (ISPOR) International Conference, Baltimore, MD. *Semi-Finalist for Research Poster Presentation Award.

Zambelli-Weiner A, Via C, Yuen M, Weiner D, Bauserman R. Difficulty of measuring dose response due to unreliability of days supply in administrative claims data. Poster presentation, 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International Conference, Baltimore, MD.

Fishbein E, Brooks EA, Piehl 2, Blaivas M, **Zambelli-Weiner A**. Understanding sepsis recognition and management in emergency room settings to improve patient outcomes. Poster presentation, 2018 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International Conference, Baltimore, MD.

April Zambelli-Weiner, Christina Via. Meta-analysis of Isotretinoin Use and Risk of Ulcerative Colitis. 2017. Poster Presentation at the 2017 American Public Health Associated, Atlanta, Georgia.

Kalatu Davies, Jennifer Judy, **April Zambelli-Weiner**, Christina Via, Agnieszka Roman, Elizabeth Brooks, Frank Vicini. Estimation of five-year local recurrence of invasive breast cancer after election intraoperative radiotherapy (IORT). Oral Presentation, 2017 American Public Health Associated, Atlanta, Georgia.

Matt Yuen, Celena Kinsey, and **April Zambelli-Weiner.** Hydraulic Fracturing and Childhood Leukemia. Oral Presentation, 2017 American Public Health Associated, Atlanta, Georgia.

Eliza Fishbein, Alisha Gray, Robert Bauserman, Jeff Elliot, **April Zambelli-Weiner**. Women's experiences with NVP and anti-emetic usage: A formative research study. Poster Presentation, 2017 American Public Health Associated, Atlanta, Georgia.

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Alisha Gray, Eliza Fishbein, Naima Abdullahi, Jill Fromewick, **April Zambelli-Weiner**, Ghenet Besera, Howard Goldberg, Mary Goodwin, Thomas Clark. Female genital mutilation/cutting and the paradigm experiences of refugee patients. Caucus on refugee and immigrant health. 2017. Poster Presentation at the 2017 American Public Health Associated, Atlanta, Georgia.

Via C, **Zambelli-Weiner A,** Bauserman R, Brooks E. Qualitative research identifies unexpected provider perceptions about noncompliance in cataract patients. Oral presentation,

American Public Health Association, November 2017, Atlanta, Georgia.

Abdullahi N, Fromewick J, Fishbein E, Gray A**, Zambelli-Weiner A,** Besera G, Goldberg H, Goodwin M. "Female genital mutilation/cutting and the paradigm experiences of refugee patients." Congress on Women's Health, April 2017, Washington DC.

Zambelli-Weiner A., Brooks E., Brolin R., Bour ES. "Total charges for postoperative leak following laparoscopic sleeve gastrectomy." Poster Presentation, American Society for Metabolic and Bariatric Surgery. Obesity Week Conference, November 2013, Atlanta, Georgia.

Moller Hikel S, Moon K, **Zambelli-Weiner A.** "Increased Risk of Childhood Leukemia in Communities Impacted by Hydraulic Fracturing in the Marcellus Shale." Oral Presentation, International Society for Environmental Epidemiology. 23rd Conference, September 2011, Barcelona, Spain.

Zambelli-Weiner A, Kramer S, Moller S, Hawkins M. "A Persistent Worldwide Environmental
Hazard: Former Manufactured Gas Plant (FMGP) Sites." Oral Presentation, International Society for Environmental Epidemiology 20th Conference, October 2008, Pasadena CA.

Arnold JW, Kramer S, **Zambelli-Weiner A**. "Assay to Measure Efficacy of Disinfectants Against *Listeria monocytogenes* Biofilms." 122nd AOAC Meeting, September 2008, Dallax TX.

Moller S, **Zambelli-Weiner A**, Hawkins M, Kramer S. "Excess Cancer Risk Among a Population Exposed to Environmental Carcinogens." Poster Presentation, Society for Epidemiologic Research 41st Annual Meeting, July 2008, Chicago, IL.

Zambelli-Weiner A, Kramer S. "Elevated Incidence of Neuroblastoma in a Community Exposed to Carcinogens from a Munitions Factory." Poster Presentation, 40th Annual Meeting of the Society for Epidemiologic Research, June 2007, Boston, Massachusetts.

Zambelli-Weiner A, Moller S, Kramer S. "Association Between Hazardous Waste from a Munitions Factory and Neuroblastoma." Poster Presentation, Twentieth Annual Meeting of the Society for Pediatric and Perinatal Epidemiologic Research, June 2007, Boston, Massachusetts.

Arnold JW, **Zambelli-Weiner A**., Kramer S. "Methods to measure control of *Listeria monocytogenes* biofilms on test materials from food production and processing facilities." Poster Presentation, American Society for Microbiology, 4th Conference on Biofilms, March 2007, Quebec City, Canada.

Zambelli-Weiner A, Stockton M, Ehrlich E, Whitmer M, Lewis D, Olenchock S, Barnes KC. Poster Presentation, "House Dust Endotoxin Exposure Mitigates Asthma Severity in a Tropical Environment." American Academy of Asthma, Allergy & Immunology, March

2004, San Francisco, California.

Munoz M, **Zambelli-Weiner A**, Grant A, Lorenzo M, Ehrlich E, Burki M, Gao L, Ye S, Beaty TH, Garcia JGN, Barnes KC. Poster Presentation, "Association Between Variants in the Gene Encoding Myosin Light Chain Kinase (MLCK) and Asthma and Atopy." American Academy of Asthma, Allergy & Immunology, March 2004, San Francisco, California.

Baltadjieva D, Berg T, **Zambelli-Weiner A**, Mathias RA, Zardkoohi O, Brummet M, Beck LA, Barnes KC. Poster Presentation, "Variants in the Gene Encoding Acyloxyloacyl Hyrdoxylase (AOAH) are Associated with Total IgE." American Academy of Asthma, Allergy & Immunology, March 2004, San Francisco, California.

Zambelli-Weiner A, Barnes KC. "The CD14-159 SNP in a Population of African Descent." Oral Presentation, "From Genome to Disease: A Symposium of High-Throughput Biology." Sponsored by NHLBI, July 2003, Bethesda, Maryland.

Zambelli-Weiner A, Maloney J, Gao L, Ye S, Garcia JGN, Barnes KC. "Association between the CD14-159 Polymorphism and Acute Lung Injury" Poster Presentation, 99th Annual Conference of the American Thoracic Society, May 2003, Seattle, Washington.

Zambelli-Weiner, A, Munoz M, Ehrlich E, Jimenez S, Caraballo L, Wills-Karp M, Barnes K. "A Novel Single Nucleotide Polymorphism in Complement Component 5 Receptor 1 (C5aR) on Chromosome 19q13.3 is not Associated with Asthma in an Afro-Caribbean Population." Poster Presentation, Johns Hopkins University Department of Medicine Research Retreat, April
2003, Baltimore, Maryland.

Ehrlich E**, Zambelli-Weiner A**, Stockton ML, Barnes KC. "The CD14(C-159T) Polymorphism and Allergic Disease in African American Families." Oral Presentation, 60th Anniversary Meeting of the American Academy of Asthma, Allergy, and Immunology, March 2003, Denver, Colorado.

Stockton ML, **Zambelli-Weiner A**, Rowell C, Levett PN, Naidu RP, Barnes KC. "High Circulating Soluble CD14 (sCD14) Levels are not Associated with Asthma or Atopy in an Afro- Caribbean Population from Barbados." Poster Presentation, 60th Anniversary Meeting of the American Academy of Asthma, Allergy, and Immunology, March 2003, Denver, Colorado.

Zambelli-Weiner A, Farkas DH, Chan V, Mathias RA, Casolaro V, Barnes KC. "The Transcriptional Factor LBP-1C/CP2/LSF Gene on Chromosome 12q13 is not Associated with Asthma in Two Independent Populations." Poster presentation, 52nd Annual Meeting of the American Society of Human Genetics, October 2002, Baltimore, Maryland.

Zambelli-Weiner A, Gray B., Levett PN, Naidu RP, Barnes KC. "The CD14(-159) Polymorphism is not Associated with Circulating sCD14 nor Total Serum IgE in an Asthmatic Population of African Descent." Poster presentation, 58th Annual Meeting of the

American Academy of Asthma, Allergy, and Immunology, March 2002, New York, New York.

Zambelli-Weiner A, Casolaro V, Nutman TB, Barnes K.C. "Cross Reactivity of T-cell responses to major allergens of cockroach and antigens from extracellular parasites in individuals with cockroach sensitization." Poster presentation, 57th Annual Meeting of the American Academy of Asthma, Allergy, and Immunology, March 2001, New Orleans, Louisiana.

12 Appendix D. List of Prior Testimony and Compensation

April Zambelli-Weiner, List of Prior Testimony

2016 Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Relevant Products Liability Litigation, MDL 2100. United States District Court, Southern District of Illinois.

2016 Accutane® Multi-County Litigation (MCL), Superior Court of New Jersey, Division: Atlantic County; Civil Action No 271

2015 Mirena® IUD Products Liability Litigation, MDL 2434. United States District Court, Southern District of New York.

2014 Richard Thomas Walsh, Executor of the Estate of Thomas J. Walsh vs. BASF Corporation et al. US District Court for the District of Pennsylvania, Civil Action No. GD 10-018588.

2012 Vioxx Products Liability Litigation, MDL Docket No. 1657. US District Court for the Eastern District of Louisiana.

Compensation Schedule

PROFESSIONAL RATE SCHEDULE JANUARY – DECEMBER 2018	
LABOR CATEGORY	**HOURLY RATES**
Research Assistant	$150.00 - $195.00
Scientist	$175.00 - $210.00
Public Health Analyst	$175.00 - $195.00
Senior Scientist	$225.00 - $300.00
Statistician	$200.00 - $225.00
Subject Matter Expert – Consulting | Testifying	$375.00 - $550.00
DEPOSITION or TRIAL	
Expert Testimony (daily or any portion thereof)	$7,500.00
Expert Testimony (daily or any portion thereof) with Travel	$8,500.00
Travel Expenses – transportation, lodging, meals, incidentals	Actual Incurred